Clodoveo Ferri

Overview of the Research Line:
from Mixed Cryoglobulinemia
(Cryoglobulinemic Vasculitis)
to HCV infection, Autoimmunity, and Oncogenesis

L'aspetto di Pisa mi piace assai
Più di quel di Firenze.
Questo Lung'arno è uno spettacolo
Così ampio, così magnifico,
Così gaio, così ridente, che innamora.
Non ho veduto niente di simile
Né a Firenze né a Milano né a Roma.
E veramente non so se in tutta l'Europa
Si trovino molte vedute di questa sorta.
Giacomo Leopardi
Pisa 12 novembre 1827

The Lungarni of Pisa

I like the look of Pisa much
more than that of Florence.
This Lungarno is a spectacle
so large. so magnificent,
so gay. so smiling. that it makes you fall in love.
I have seen nothing similar
neither in Florence nor in Milan nor in Rome.
And I really do not know if in all of Europe
one finds many views of this kind.
Glacomo Leopardi

Pisa 12 novembre 1827

November 1821. Perry B. Shelley to Lord Byron

”Stand on the marble bridge, cast your eye, if you are not dazzled, on its river glowing as with fire, then follow the graceful curve of the palaces on the Lung’Arno …
and tell me if any thing can surpass a sunset at Pisa”

Summary

Since the early seventies, Prof. Clodoveo Ferri has conducted numerous clinical and etiopathogenetic studies on a large Italian case series of patients with mixed cryoglobulinemia (MC), synonym cryoglobulinemic vasculitis (CV), in close collaboration with Prof. Stefano Bombardieri and Gianpiero Pasero and numerous other Italian and foreign experts.

Starting from MC, the overall body of researches includes (see Figure and comments on page 5 and 6):

1970s-1980s -> clinical-immunological studies on cryoprecipitation, hepatic, renal, neurological and pulmonary involvement of MC, role of 'indolent' lymphoproliferation underlying cryoglobulinemic syndrome

1991 -> first demonstration of the close association between hepatitis C virus infection and MC by HCV RNA detection

1993 -> studies on HCV lymphotropism, which in addition to its hepatotropism is able to infect and stimulate (over-expression of Bcl2) peripheral lymphocytes in patients with HCV-associated MC

1994 -> first demonstration of a significant association between HCV infection and 'idiopathic' B-cell NHL

in the following years -> numerous studies focused on the role of HCV in various immune-mediated disorders, organ- and non-organ-specific (thyroid, pancreas, porphyria cutanea tarda, etc.), as well malignancies (papillary thyroid carcinoma, in addition to to B-NHL and hepatocellular carcinoma)

moreover: survival studies on MC pts, diagnostic and therapeutic guidelines, and more recently the evaluation of the impact of the COVID-19 pandemic on 450 patients with MC.

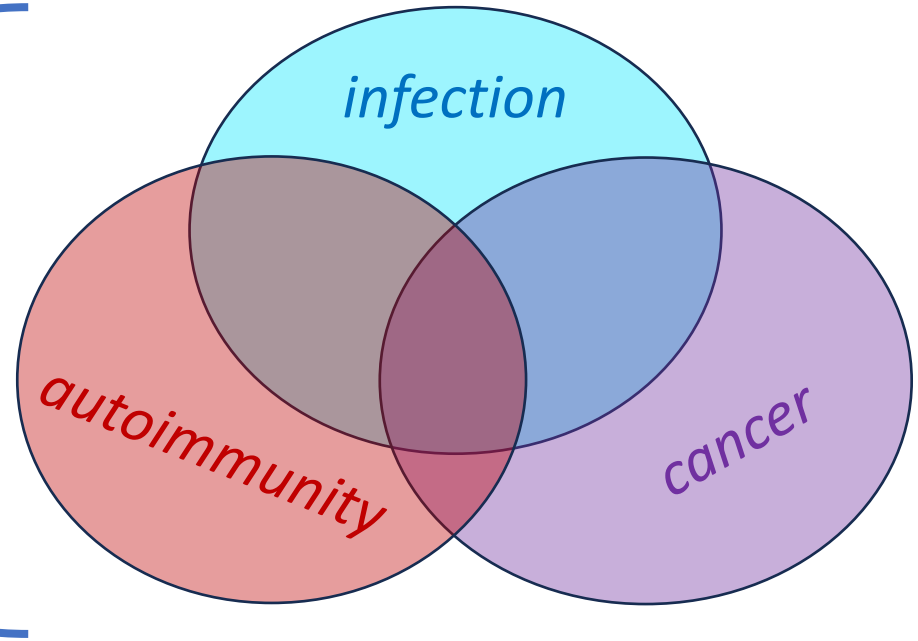
The long research activity for over 50 years has produced a large body of knowledge and pioneering studies, also thanks to fruitful collaborations with other recognized experts.
The history of MC starts from the early decades of the 20th century, initially as well-known 'laboratory curiosity', the immuno-cryoprecipitation, associated with seropositivity for rheumatoid factor (RF) and complement consumption; these serological abnormalities, very often without apparent clinical significance, only in some subjects lead to the **clinical triad arthralgia/asthenia/vasculitic purpura.** The presence of these symptoms, including serum FR+, suggested a specific clinical syndrome well codified in the 1960s by Meltzer M and Franklin EC (Am J Med. 1966). In the absence of known causes/clinical associations in the majority of patients the **MC syndrome** was classified as 'essential'.
The numerous clinical-pathological facets of the MC syndrome have suggested a series of studies in different fields, involving, in addition to rheumatologists, various specialists, such as virologists, internists, immunologists, hematologists, hepatologists, nephrologists, neurologists, etc.

The results of researches recorded so far are of great relevance for various aspects, in particular:

- **biological field:** the demonstration of etiopathogenetic link underlying the symptomatic complex 'Infection-autoimmunity-lymphoproliferation-cancer'

- **clinical practice:** the eradication of the common viral triggering agent (HCV) can lead in many subjects to the remission of the autoimmune-vasculitic syndrome and/or malignant lymphoproliferation.

Mixed Cryoglobulinemia & HCV
a model of
infection, autoimmunity, and oncogenesis



The history of this multistep research line, moving towards different directions, may be useful for many aspects, in particular

- ***it may have a stimulating and educational value, especially for students, young researchers, and clinicians***
- ***it underlies the relevance in the clinical practice to deal with the complexity requiring a multidisciplinary approach***

Editorial

Mixed cryoglobulinaemia and hepatitis C virus: a paradigm of a virus-related autoimmune and lymphoproliferative disorder

C. Ferri[1], S. Bombardieri[2]

Clin Exp Rheumatol 2021; 39: 1265-1268.

from Mixed Cryoglobulinemia (Cryoglobulinemic Vasculitis)
to HCV infection, Autoimmunity,
and Oncogenesis.
1972 -2024

multistep process

Mixed cryoglobulinaemia and hepatitis C virus: a paradigm of a virus-related autoimmune and lymphoproliferative disorders

Ferri C, Bombardieri S
Clin Exp Rheumatol 2021

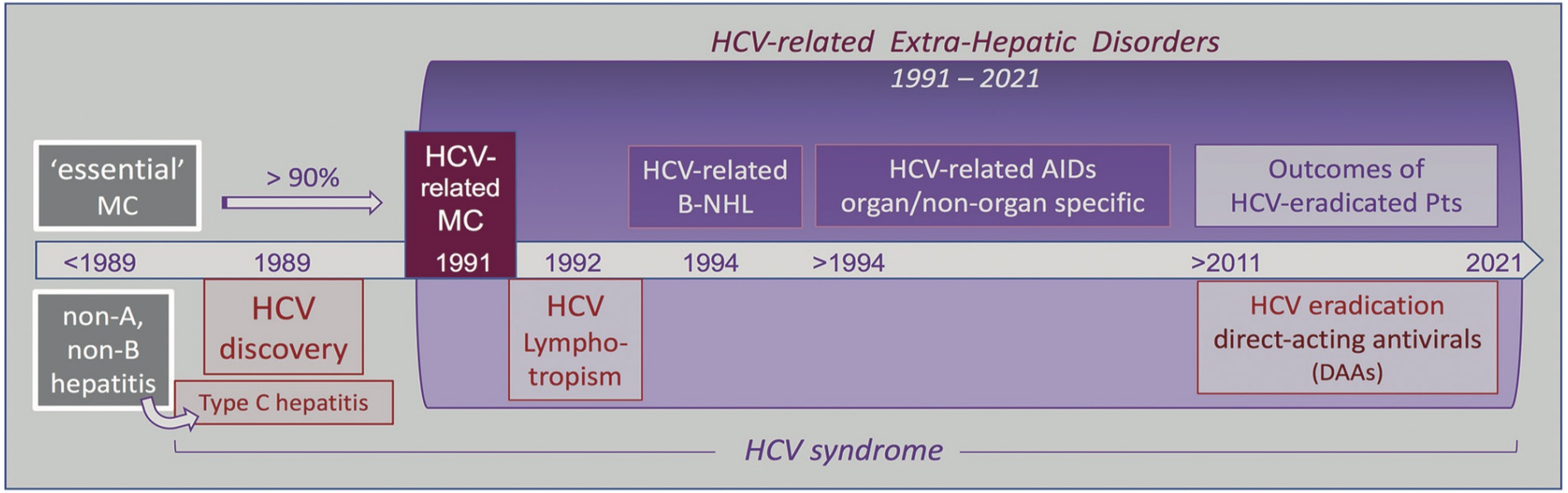


Fig. 1. Schematic representation of thirty-year history of HCV-related mixed cryoglobulinaemia and other HCV-related extra-hepatic disorders (HCV-EHDs). Following the HCV discovery (1989), the striking association between HCV and mixed cryoglobulinaemia (MC), synonymous with cryoglobulinaemic vasculitis, was demonstrated in 1991. Both dates represent a fundamental turning point in the history of two disorders previously classified of unknown aetiology: the so-called non-A, non-B hepatitis and the 'essential' MC. The association HCV-MC opened a fruitful succession of clinical-epidemiological, virological, and pathological studies that over the last three decades led to the definition of HCV-related extra-hepatic disorders (HCV-EHDs), a complex of autoimmune organ- and non-organ-specific, and lymphoproliferative disorders, mainly B-cell non-Hodgkin lymphoma (B-NHL).

HCV syndrome' consists of the aggregation of

- HCV-related hepatic manifestations (hepatitis C, cirrhosis, hepatocellular carcinoma) and
- HCV extra-hepatic disorders: MC syndrome, B-NHL, endocrine disorders, porphyria cutanea tarda, etc.

More recently we are experiencing another revolution following the introduction of direct-acting antivirals (DAAs), able to eradicate the HCV. However, many issues still remain open, especially as regards the persistence or relapses/flares of different HCV-EHDs, mainly the cryoglobulinaemic vasculitis and B-NHL despite HCV eradication.

from Mixed Cryoglobulinemia (Cryoglobulinemic Vasculitis) to HCV infection, Autoimmunity, and Oncogenesis.
1972 -2024

multistep process

1966
Definition Mixed Cryo. (MC) or Cryo. Vasculitis

1979
Bombardieri S – Ferri C
High % of chronic hepatitis in MC pts
Possible hepatotropic viral triggers. (Low prevalence of HBV)

1989
HCV discovery

1990
Ferri -Pascual
Ab anti-HCV in MC pts (<50%)

1991
Ferri C
First report HCV viremia (HCV RNA) In 86% of MC
Arthr. Rheum / Clin Exp Rhe

1994
Ferri C
First report Association HCV – NHL
JAMA / Br J Haematol

1992-93
Fargion - Ferri
Role of HCV in **Porfiria Cutanea Tarda**

1999…
Ferri – Antonelli
Role of HCV **Thyroiditis/ Thyroid cancer & diabetes**

2022
Ferri – Gragnani- Zignego
Effects of HCV eradication on MC syndrome & B-NHL impactt of COVID19 pandemic

Since 1991 over 30-year history
HCV-related mixed cryoglobulinemia and other extra-hepatic disorders

HCV-related Extra-Hepatic Disorders
1991 – 2021

'essential' MC
> 90%
HCV-related MC
1991
HCV-related B-NHL
HCV-related AIDs organ/non-organ specific
Outcomes of HCV-eradicated Pts

<1989 | 1989 | 1992 | 1994 | >1994 | >2011 | 2021

non-A, non-B hepatitis
HCV discovery
Type C hepatitis
HCV Lympho-tropism
1992-1993
Zignego - Ferri
2002
Zignego - Ferri
Bcl2 0verexpression
HCV eradication direct-acting antivirals (DAAs)

HCV syndrome

1971
Heimann R.
Pres. Eur. Society Pathology
Association liver cirrhosis and lymphoproliferative disorders
Lancet 1971

see Heimann letters. --> Ferri

1996
Haematologica Editorial
HEPATIS C VIRUS: A LINKAGE BETWEEN HEMATOLOGY AND HEPATOLOGY ESTABLISHED THROUGH MAJOR CONTRIBUTIONS BY ITALIAN RESEARCH

Ionian Sea

From internal medicine to rheumatology and back: the example of mixed cryoglobulinemia

Pasero GP, Bombardieri S, Ferri C
Clin Exp Rheumatol 1995 Jan-Feb;13(1):1-5.

Seventies-Eighties

First key observation

- **High prevalence of liver involvement in patients with mixed cryoglobulinemia**
  (from chronic hepatitis to cirrhosis/hepatocellular carcinoma)
  Of note, liver involvement is a rare complication in the course of other systemic vasculitides

- **This finding suggested a possible causal role of 'hepatotropic' infectious agent(s) in patients with mixed cryoglobulinemia**

Meltzer M, et al. Am J Med 1966; Bombardieri S, Ferri C, et al. Ric Clin Lab 1979; Gorevic PD, et al. Am J Med 1980

Seventies-Eighties

- **The high prevalence of liver** involvement (from chronic hepatitis to cirrhosis, and hepatocellular carcinoma) in patients with mixed cryoglobulinemia or cryoglobulinemic vasculitis (of note, chronic hepatitis is a rare organ complication in the course of other systemic vasculitides) **suggested the possible causal role of a 'hepatotropic' infectious agent.**

- **HBV** could represent a likely candidate also in light of its role in patients affected by another form of systemic vasculitis, the polyarteritis nodosa, described since the early seventies.
- However, the **low prevalence of HBV infection in patients with mixed cryoglobulinemia** (with/without chronic hepatitis) led to exclude its role in the majority of patients.
- **Before the discovery of HCV (1989), many 'idiopathic' hepatitis were classified as 'nonA, nonB hepatitis' and mixed cryoglobulinemia as 'essential' MC**

(see figure page 7 & 8)

Ric Clin Lab 1979

Liver involvement in essential mixed cryoglobulinemia

S Bombardieri, C Ferri, O Di Munno, G Pasero

Abstract

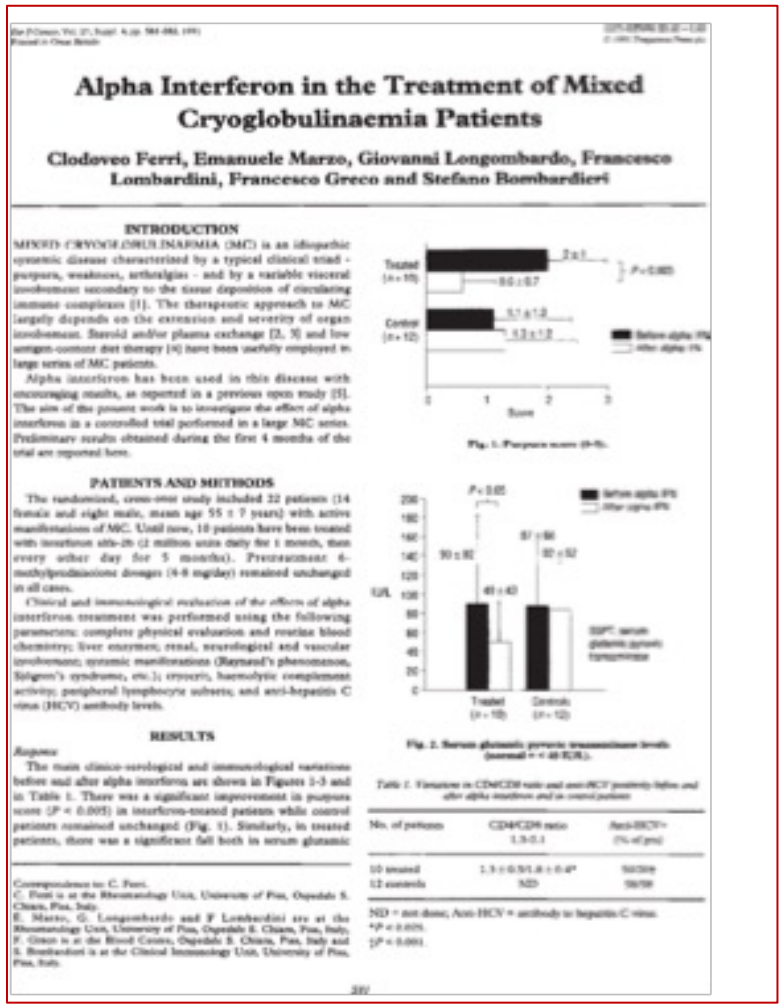
Twenty-one of 30 patients with essential mixed cryoglobulinemia (EMC) had evidence of liver involvement.
The liver disease was characterized by the absence of clinical symptoms, hepatosplenomegaly, mild elevation
of enzymes, abnormal BSP retention and low albumin levels. Histology, available in 12 patients, showed either
chronic persistent or chronic active hepatitis or liver cirrhosis; 44% of the patients had HBsAg or HBsAb
in sera and/or cryoglobulins, confirming the high frequency of exposure to hepatitis B virus (HBV) infection i
n EMC. However, liver lesions were similar in all patients, regardless of HBV exposure. Since other factors
usually associated with chronic liver diseases were absent or apparently irrelevant, it is temptative to
speculate that a 'cryoglobulinemic hepatitis' may exist as a distinct syndrome. The characteristic complement
profile of the patients with EMC (low CH50 and C4, normal C3PA), not related to albumin levels, can help to
differentiate this disease from chronic liver disease without cryoglobulins.

Soon after the discovery of HCV (1989),
as the main cause of non-A, non-B hepatitis,
in 1990 two preliminary observations
on a limited number of patients with
Mixed Cryoglobulinemia
highlighted the presence of serum antibodies
(detected by first generation RIBA)
However, the increased prevalence of anti-HCV
remained less than 50% of patients

1990

-Pascual M et al, Hepatitis C virus in patients with cryoglobulinemia type II. *J Infect Dis* 1990

-Ferri C et al. Alpha-interferon in the treatment of mixed cryoglobulinemia patients.
International Cancer Update.
Focus on Interferon Alfa 2b. Cannes, France.
November 1-4, 1990. Proceedings
(Eur J Cancer 1991; **27**: 81-82
DOI: 10.1016/0277-5379(91)90583-Y)



Alpha Interferon in the Treatment of Mixed Cryoglobulinaemia Patients

Clodoveo Ferri, Emanuele Marzo, Giovanni Longombardo, Francesco Lombardini, Francesco Greco and Stefano Bombardieri

INTRODUCTION

PATIENTS AND METHODS

RESULTS

1991

The two preliminary observations (1990) of increased prevalence of anti-HCV antibodies were confirmed on a larger case series of patients with MC

Ferri C et al. A&R 1991

BRIEF REPORT

Arthritis & Rheumatology

ANTIBODIES TO HEPATITIS C VIRUS IN PATIENTS WITH MIXED CRYOGLOBULINEMIA

CLODOVEO FERRI, FRANCESCO GRECO, GIOVANNI LONGOMBARDO, PIERO PALLA, ADOLFO MORETTI, EMANUELE MARZO, PIER VITTORIO FOSELLA, GIAMPIERO PASERO, and STEFANO BOMBARDIERI

The prevalence of antibodies to hepatitis C virus (HCVAb) was investigated in 52 unselected patients with mixed cryoglobulinemia and in 84 patients with other systemic immunologic diseases. HCVAb were detected by an enzyme-linked immunosorbent assay, and their specificity was evaluated by a recombinant-based immunoblot assay. The presence of HBV-related markers was investigated in the same samples. HCVAb were found in 54% of mixed cryoglobulinemia patients, and the finding was confirmed by recombinant-based immunoblot assay in all cases. HCVAb and/or HBV markers were present in 70% of the patients. HCVAb seropositivity was significantly more frequent in mixed cryoglobulinemia patients with biopsy-proven liver involvement ($P < 0.01$) and with increased serum transaminase levels ($P < 0.01$). HCVAb were virtually absent in control patients with other immunologic diseases. These results support the notion that viral agents, i.e., HCV and possibly HBV, have a role in the pathogenesis of mixed cryoglobulinemia patients.

From the Rheumatology Unit and Clinical Immunology Unit, University of Pisa, and the Blood Center, Ospedale S. Chiara, Pisa, Italy.

Clodoveo Ferri, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Francesco Greco, MD: Ospedale S. Chiara; Giovanni Longombardo, BS: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Piero Palla, MD: Blood Center, Ospedale S. Chiara; Adolfo Moretti, MD: Blood Center, Ospedale S. Chiara; Emanuele Marzo, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Pier Vittorio Fosella, MD: Blood Center, Ospedale S. Chiara; Giampiero Pasero, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa; Stefano Bombardieri, MD: Rheumatology Unit and Clinical Immunology Unit, University of Pisa.

Address reprint requests to Clodoveo Ferri, MD, Istituto di Patologia Medica I, Via Roma, 67, 56100 Pisa, Italy.

Submitted for publication November 29, 1990; accepted in revised form June 27, 1991.

Mixed cryoglobulinemia is a systemic disorder characterized by a typical clinical triad—purpura, weakness, and arthralgias—and by visceral complications such as liver and renal involvement (1). The pathogenesis of vascular and parenchymal injury in this disease can be related to deposition of circulating immune complexes (1,2); however, less information is available on the etiologic factor(s). Previous exposure to hepatitis B virus (HBV) in mixed cryoglobulinemia has been reported by some authors, though the prevalence of this association varies among the reports (1–3). Based on this association, it has been hypothesized that mixed cryoglobulinemia, like arthritis and polyarteritis (4,5), might be one of the extrahepatic manifestations of HBV infection. The finding of cryoglobulins in a variety of infectious diseases and the HBV seropositivity found in some mixed cryoglobulinemia patients support the possibility that mixed cryoglobulinemia may result from a number of types of infection in predisposed individuals. Since hepatitis C virus infection is responsible for a large proportion of non-A, non-B posttransfusion hepatitis and "autoimmune" chronic hepatitis (6,7), and since liver involvement is one of the most frequent manifestations of mixed cryoglobulinemia (1–3), we investigated the prevalence of anti–hepatitis C virus antibodies (HCVAb) and their correlation with clinical and serologic parameters in a large series of unselected patients with mixed cryoglobulinemia.

Patients and methods. Two hundred patients with mixed cryoglobulinemia were followed at the Rheumatology Unit of the University of Pisa between 1972 and 1990. Of these, 52 consecutive, unselected patients who attended the clinic for routine outpatient visits between March 1990 and October 1990 were

1991

In the same year
the first demonstration
of a high prevalence (86%)
of HCV infection (viremia)
in patients with
Mixed Cryoglobulinemia

Serum HCV RNA
was assessed
by polymerase chain reaction technique
at Wellcome Diagnostics, London UK

Ferri C et al. Clin Exp Rheumatol 1991

Clin Exp Rheumatol 1991 Nov-Dec; 9(6): 621-4.

Association between hepatitis C virus and mixed cryoglobulinemia

C Ferri [1], F Greco, G Longombardo, P Palla, A Moretti, E Marzo, A Mazzoni, G Pasero, S Bombardieri, P Highfield, Corbishley T

Abstract

The prevalence of hepatitis C virus (HCV) RNA and of antibodies to HCV in an unselected series of 42 mixed cryoglobulinemia patients was investigated in this study.

HCV RNA was detected by the polymerase chain reaction technique, and HCV antibodies by two enzyme-linked immunosorbent assays (Chiron ELISA HCV, Second Generation, Emeryville CA, USA; Wellcome Diagnostic, England).

HCV RNA was found in 86% of the mixed cryoglobulinemia patients. Using either the Chiron ELISA or the Wellcome ELISA, HCV antibodies were present in 90% of the same samples; anti-HCVAb seropositivity was confirmed in all cases by immunoblot assay (Chiron RIBA HCV, Second Generation Assay).

A striking correlation between HCV RNA and anti-HCV antibody seropositivities was recorded. HCV RNA in mixed cryoglobulinemia patients was not correlated with the presence or absence of biopsy-proven liver involvement.

These results suggest that the association between HCV and mixed cryoglobulinemia is not fortuitous, and therefore that HCV may have an etiopathogenetic role in this disorder.

1992-93

An important step in the study of the etiopathogenetic role of HCV in autoimmune diseases (organ- and non-organ-specific) and in lymphoproliferative disorders was the

➡ **discovery of HCV lymphotropism**

(in addition to its well known hepatotropism) demonstrated in either

- Pts with isolated hepatitis C
  and
- Mixed Cryoglobulinemia pts

Infection of peripheral mononuclear blood cells by hepatitis C virus.

Zignego AL, Macchia D, Monti M, Thiers V, Mazzetti M, Foschi M, Maggi E, Romagnani S, Gentilini P, Bréchot C.

J Hepatol. 1992 Jul; 15(3): 382-6.

Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia

C Ferri[1], M Monti, L La Civita, G Longombardo, F Greco, G Pasero, P Gentilini, S Bombardieri, A L Zignego

Blood 1993 Dec 15; 82(12): 3701-4.

Infection of Peripheral Blood Mononuclear Cells by Hepatitis C Virus in Mixed Cryoglobulinemia

By Clodoveo Ferri, Monica Monti, Luca La Civita, Giovanni Longombardo, Francesco Greco, Giampiero Pasero, Paolo Gentilini, Stefano Bombardieri, and Anna Linda Zignego

A striking association between hepatitis C virus (HCV) infection and mixed cryoglobulinemia (MC) has been shown; thus, HCV seems to play an important etiopathogenetic role in this lymphoproliferative disorder. Because HCV is both a hepatotropic and lymphotropic virus, this study aimed to investigate the prevalence of HCV infection of peripheral blood mononuclear cells (PBMCs) in a series of 16 patients with type II (IgMk) MC. Antibodies against HCV were detected by commercially available kits (Second Generation Chiron enzyme-linked immunosorbent assay [ELISA] and recombinant-based immunoblot assay [RIBA]), and the presence of HCV RNA was evaluated in both sera and isolated PBMCs using the polymerase chain reaction technique. A previous exposure to HCV was shown by ELISA and confirmed by RIBA in all cases (100%). Moreover, HCV RNA was present in the sera of 8 of 16 patients (50%), whereas its frequency markedly increased (13 of 16 [81%]) when genomic sequences were detected in peripheral lymphocytes. HCV RNA was never detected in the PBMCs of 20 control subjects. These findings showed that HCV infection, alone or in combination with other factors, may be responsible for the clonal B-cell expansion underlying the systemic manifestations of MC, and may explain the appearance of a malignant non-Hodgkin's lymphoma in some subjects.

© *1993 by The American Society of Hematology.*

New England

The knowledge acquired in the early nineties has led to

1991-1994

Second key observation

1. *MC is frequently associated with HCV infection*
2. *HCV is a lymphotropic virus*
3. *MC can be complicated by B-NHL*

on the basis of which a question arose:

What is the role of HCV in the etiopathogenesis of so-called 'idiopathic' B-NHL?

What is the role of HCV in the pathogenesis of so-called 'idiopathic' B-NHL?

1994

First description of the association HCV & B-cell Non-Hodgkin's lymphoma

In unselected series of patients with 'idiopathic' B-cell NHL referred to Hematology Unit of University of Pisa, Italy

HCV-related markers (anti-HCV/HCV RNA by PCR) were detected **in 34%** **of unselected B-NHL patients;** this prevalence is particularly significant when compared with HCV prevalence in Hodgkin's lymphoma (3%) and healthy controls (1.3%).

JAMA. 1994 Aug 3;272(5):355-6. doi: 10.1001/jama.1994.03520050033023.

Non-Hodgkin's lymphoma: possible role of hepatitis C virus

C Ferri, L La Civita, F Caracciolo, A L Zignego

Br J Haematol
1994 Oct;88(2):392-4.
doi: 10.1111/j.1365-2141.1994.tb05036.x.

Hepatitis C virus infection in patients with non-Hodgkin's lymphoma

C Ferri[1], F Caracciolo, A L Zignego, L La Civita, M Monti, G Longombardo, F Lombardini, F Greco, E Capochiani, A Mazzoni, et al.

2002

In collaboration with
Prof. AL Zignego
Univ. of Florence, Italy

Demonstration of frequent activation of the proto-oncogene Bcl2 (t14; 18) translocation) in patients with MC with/without B-cell NHL

This finding supports the oncogenetic role of HCV and, at the same time, it strengthens the role of mixed cryoglobulinemia as pre-neoplastic condition

Annals of Internal Medicine®

Articles | 1 October 2002

Prevalence of *bcl-2* Rearrangement in Patients with Hepatitis C Virus–Related Mixed Cryoglobulinemia with or without B-Cell Lymphomas

Anna Linda Zignego, MD, PhD ✉, Clodoveo Ferri, MD, Francesca Giannelli, PhD, Carlo Giannini, PhD, ... See Mo

Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: A meta-analysis of epidemiological studies

Cancer Sci. 2004 Sep;95(9):745-52. doi: 10.1111/j.1349-7006.2004.tb03256.x.

Keitaro Matsuo,[1, 3, 5] Aaron Kusano,[3] Aravind Sugumar,[4] Shigeo Nakamura,[2] Kazuo Tajima[1] and Nancy E. Mueller[3]

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[3]Department of Epidemiology, [4]Master of Public Health in Qu
02115, USA

(Received May 27, 2004/Revised July 14, 2004/Accepted July

Studies on the **HCV & B-NHL association** published in the first 10 years following its first description in 1994

Table 1. Summary of studies that have examined the association between HCV infection and non-Hodgkin's lymphoma

	Country	Cases (*n*)	HCV positive case (*n*)	Case description	B-NHL subgroup analysis	T-NHL subgroup analysis	Control (*n*)	HCV positive control (*n*)	Control descrption	Matching	HCV tests
Ferri *et al.* (1994)	Italy	50	15	B-cell NHL only	Yes	No	30	1	Hospital-based control	Age	2G ELISA and RIBA
Silvestri *et al.* (1996)	Italy	366	31	NHL	Yes	Yes	6917	199	Population-based control in a cohort	No	2G EIA and RIBA
Musto *et al.* (1996)	Italy	150	40	NHL	No	No	466	25	Hospital-based control	No	3G ELISA
Mazzaro *et al.* (1996)	Italy	199	57	NHL	No	No	6917	199	Population-based control in a cohort	No	2G EIA and RIBA
De Rosa *et al.* (1997)	Italy	100	21	NHL	Yes	Yes	1568	30	Blood donor control	No	3G ELISA and RIBA
Zuckerman *et al.* (1997)	USA	131	22	NHL	Yes	Yes	114	4	Hospital-based control	No	2G ELISA
Shariff *et al.* (1999)	Canada	125	2	NHL	Yes	Yes	1085	11	Healthcare workers	No	3G EIA+RIBA
Paydas *et al.* (1999)	Italy	98	9	NHL	No	No	36,418	192	Blood donor control	No	3G ELISA
Vallisa *et al.* (1999)	Italy	175	65	B-cell NHL only	Yes	No	175	10	Hospital-based control	Age, sex	3G ELISA and RIBA
Pioltelli *et al.* (2000)	Italy	300	48	B-cell NHL only	Yes	No	600	51	Hospital-based control	No	3G ELISA and RIBA
Zucca *et al.* (2000)	Switzerland	180	17	B-cell NHL only	Yes	No	5424	49	Blood donor control	No	3G ELISA
Mizorogi *et al.* (2000)	Japan	125	17	NHL	Yes	Yes	452	18	Hospital-based control	No	2G EIA
Harakati *et al.* (2000)	Saudi Arabia	56	12	B-cell NHL only	Yes	No	104	3	Hospital-based control	No	2G EIA
Hausfater *et al.* (2001)	France	164	3	B-cell NHL only	Yes	No	694	3	Hospital-based control	No	3G ELISA
Kuniyoshi *et al.* (2001)	Japan	348	20	NHL	No	No	1,513,358	11,396	Blood donor control	No	3G ELISA
Montella *et al.* (2001)	Italy	111	28	NHL	Yes	Yes	226	17	Hospital-based control	No	3G ELISA
Rabkin *et al.* (2002)	USA	59	2	B-cell NHL only	Yes	No	95	0	Control drawn from same cohort	Age, sex	3G ELISA
Kaya *et al.* (2002)	Turkey	70	1	NHL	No	No	70	0	Healthy subjects	Age, sex	3G EIA
Imai *et al.* (2002)	Japan	187	23	NHL	Yes	Yes	197,600	10,176	Blood donor control	Age, sex	2G and 3G ELISA
Chindamo *et al.* (2002)	Brazil	109	10	NHL	Yes	Yes	39,371	472	Blood-donor-control	No	2G and 3G ELISA
Mele *et al.* (2003)	Italy	400	70	B-cell NHL only	Yes	No	396	22	Hospital-based control	No	3G EIA+RIBA
Avires *et al.* (2003)	Mexico	416	2	B-cell NHL only	Yes	No	832	1	Blood donor control	Age, sex	3G ELISA+RIBA
Iwata *et al.* (in press)	Japan	130	5	NHL	Yes	Yes	568	29	Hospital-based control	Age, sex	1G or 2G EIA

Abbreviations: ELISA, enzyme-linked-immunosorbent assay; EIA, enzyme-immunoassay; and RIBA, recombinant immunoblot assay. 2G and 3G stand for second generation and third generation, respectively.

little lunch in Tuscany

To my beloved father Paolo, my uncle Vincenzo Cardaci, and the dog Jurgen

1989 Summer

1993

European Journal of Clinical Investigation

First published: December 1993
https://doi.org/10.1111/j.1365-2362.1993.tb00741

Study on

Etiopathogenetic role of HCV in patients with porphyria cutanea tarda through a possible virus-induced autoimmune mechanism

In collaboration with prof.
M. P. Manns immuno-hepatologist
University of Hannover, Germany

Hepatitis C virus-related autoimmunity in patients with porphyria cutanea tarda

C. FERRI, U. BAICCHI, L. LA CIVITA, F. GRECO, G. LONGOMBARDO, A. MAZZONI, G. CARECCIA, S. BOMBARDIERI, G. PASERO, A. L. ZIGNEGO, M. P. MANNS

Abstract

Hepatitis C virus (HCV) infection is frequently found in autoimmune hepatitis and mixed cryoglobulinaemia. In these conditions HCV could be responsible for immuno-mediated organ alterations. The aim of this study was to evaluate the presence of immunological alterations in PCT patients, in which HCV infection has been frequently found. Twenty-three PCT patients were evaluated for clinical and serological alterations, including: chronic hepatitis, other systemic symptoms, serum cryoglobulins and rheumatoid factor (RF), haemolytic complement, serum immunoglobulins, anti-nuclear (ANA), anti-smooth muscle (ASMA), anti-liver-kidney-microso-mal (anti-LKMI), anti-soluble-liver-antigen (SLA), anti-mitochondrial (AMA), anti-GOR antibodies, anti-HCV and HCV RNA. Abnormal serum ALT were present in the majority of cases (20/23, 87%), while liver biopsy revealed a chronic persistent hepatitis or chronic active hepatitis in 15/20 (75%) PCT patients. In a high percentage of subjects (91%) the presence of anti-HCV was detected by ELISA and RIBA II (Chiron, Emeryville CA, USA). In 17/22 (77%) cases the ongoing HCV replication in the serum was demonstrated by the detection of HCV genomes (polymerase chain reaction). The prevalence of both anti-HCV and HCV RNA in PCT was significantly higher if compared to 22 systemic immunological diseases ($P<$ 0.00l) and 47 healthy subjects ($P<0.001$). A possible HCV-induced autoimmunity In PCT was suggested by the presence of the following immunological parameter alterations: anti-GOR in 13/23 (57%), ANA in 4/23 (17%), ASMA in 18/23 (78%), anti-LKMI in 1/23 (4%), RFin 23/23 (100%), mixed cryoglobulins in 4/23 (170/0), complement consumption in 10/23 (43%). The high prevalence of HCV infection and various immunological abnormalities suggest that HCV in combination with other factors (genetic, alcohol, etc.) could play a relevant role in the pathogenesis of hepatic and metabolic alterations of PCT.

1999

First demonstration of the association

HCV infection

and

Papillary Thyroid Cancer

JAMA
The Journal of the American Medical Association

JAMA, 1999 May 5;281(17):1588.
doi: 10.1001/jama.281.17.1588.

Thyroid cancer in patients with hepatitis C infection

A Antonelli, C Ferri, P Fallahi

PMID: 10235149
DOI: 10.1001/jama.281.17.1588

Studies on the relationship

HCV infection & Endocrine Disorders

Rheumatology (Oxford), 2004 Feb;43(2):238-40.
doi: 10.1093/rheumatology/keh011.

Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients

A Antonelli[1], C Ferri, P Fallahi, M Sebastiani, C Nesti, L Barani, R Barale, E Ferrannini

Autoimmunity Reviews, 2008 Oct;8(1):18-23.
doi: 10.1016/j.autrev.2008.07.017.

Immunopathogenesis of HCV-related endocrine manifestations in chronic hepatitis and mixed cryoglobulinemia

Alessandro Antonelli[1], Clodoveo Ferri, Silvia Martina Ferrari, Michele Colaci, Poupak Fallahi

Studies on the relationship

HCV infection & Endocrine Disorders

JAMA
The Journal of the American Medical Association

JAMA 2002 Aug 14;288(6):698-9.
doi: 10.1001/jama.288.6.698.

Erectile dysfunction and hepatitis C virus infection

Clodoveo Ferri, Maria Antonella Bertozzi, Anna Linda Zignego

• DOI: 10.1001/jama.288.6.698

Camargue

2015

This review focused on
the numerous
clinical & laboratory studies
on different
HCV-related disorders
following the first demonstration of
HCV-associated MC & B-NHL

The complex of these
organ and non-organ specific
autoimmune disorders
and lymphoproliferative/neoplastic
conditions
can be termed

HCV syndrome

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DOI: 10.4254/wjh.v7.i3.327

World J Hepatol 2015 March 27; 7(3): 327-343
ISSN 1948-5182 (online)
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REVIEW

HCV syndrome: A constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer

Clodoveo Ferri, Marco Sebastiani, Dilia Giuggioli, Michele Colaci, Poupak Fallahi, Alessia Piluso, Alessandro Antonelli, Anna Linda Zignego

Clodoveo Ferri
Overview of the Research Line: from Mixed Cryoglobulinemia (Cryoglobulinemic Vasculitis) to HCV infection, Autoimmunity, and Oncogenesis.
1972 -2024

Etiopathogenesis & Therapeutic Strategies of HCV-related diseases

2015

This review focused on
the numerous
clinical & laboratory studies
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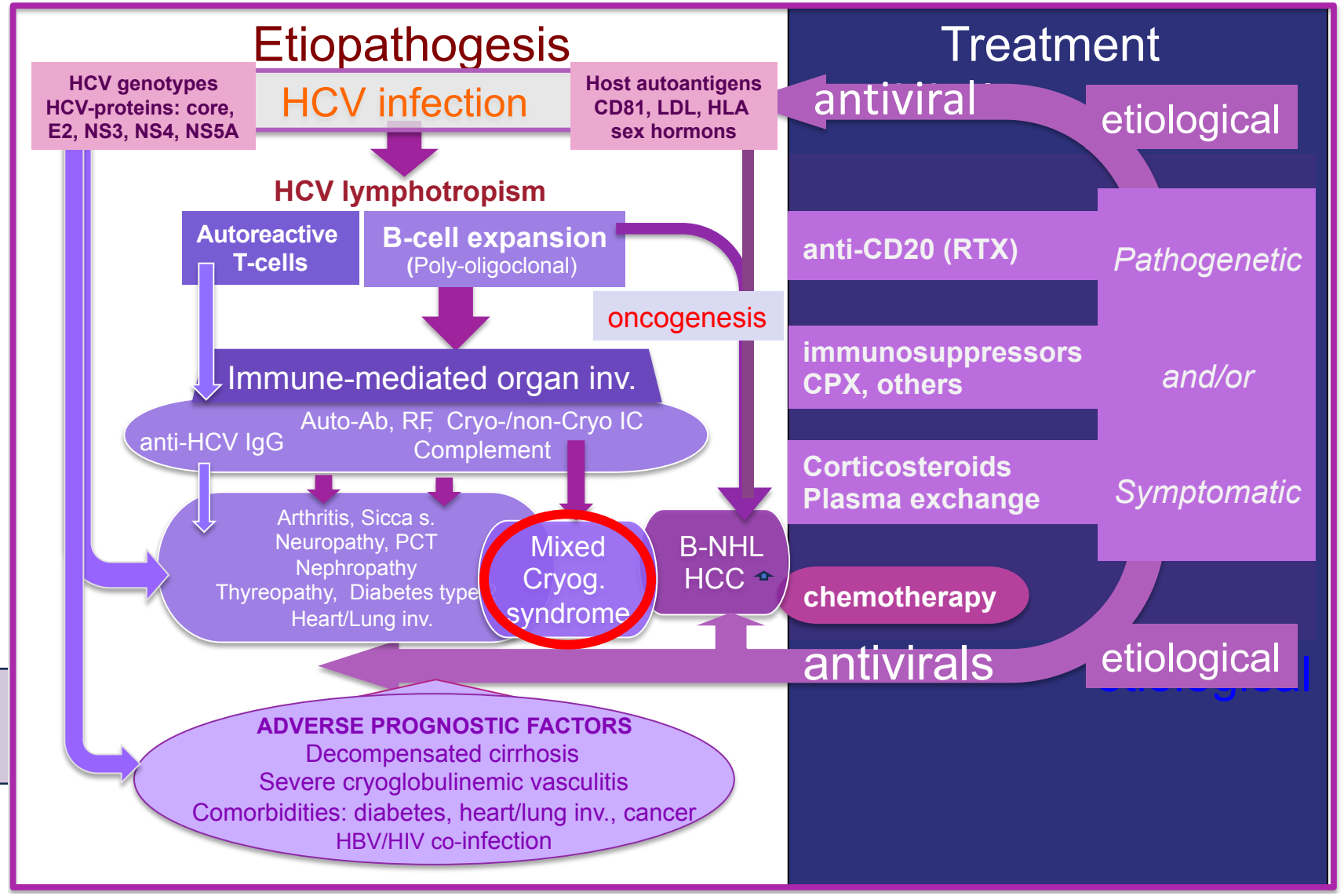
HCV-related disorders
following the first demonstration of
HCV-associated MC & B-NHL

The complex of these
organ and non-organ specific
autoimmune disorders
and lymphoproliferative/neoplastic
conditions
can be termed

HCV syndrome

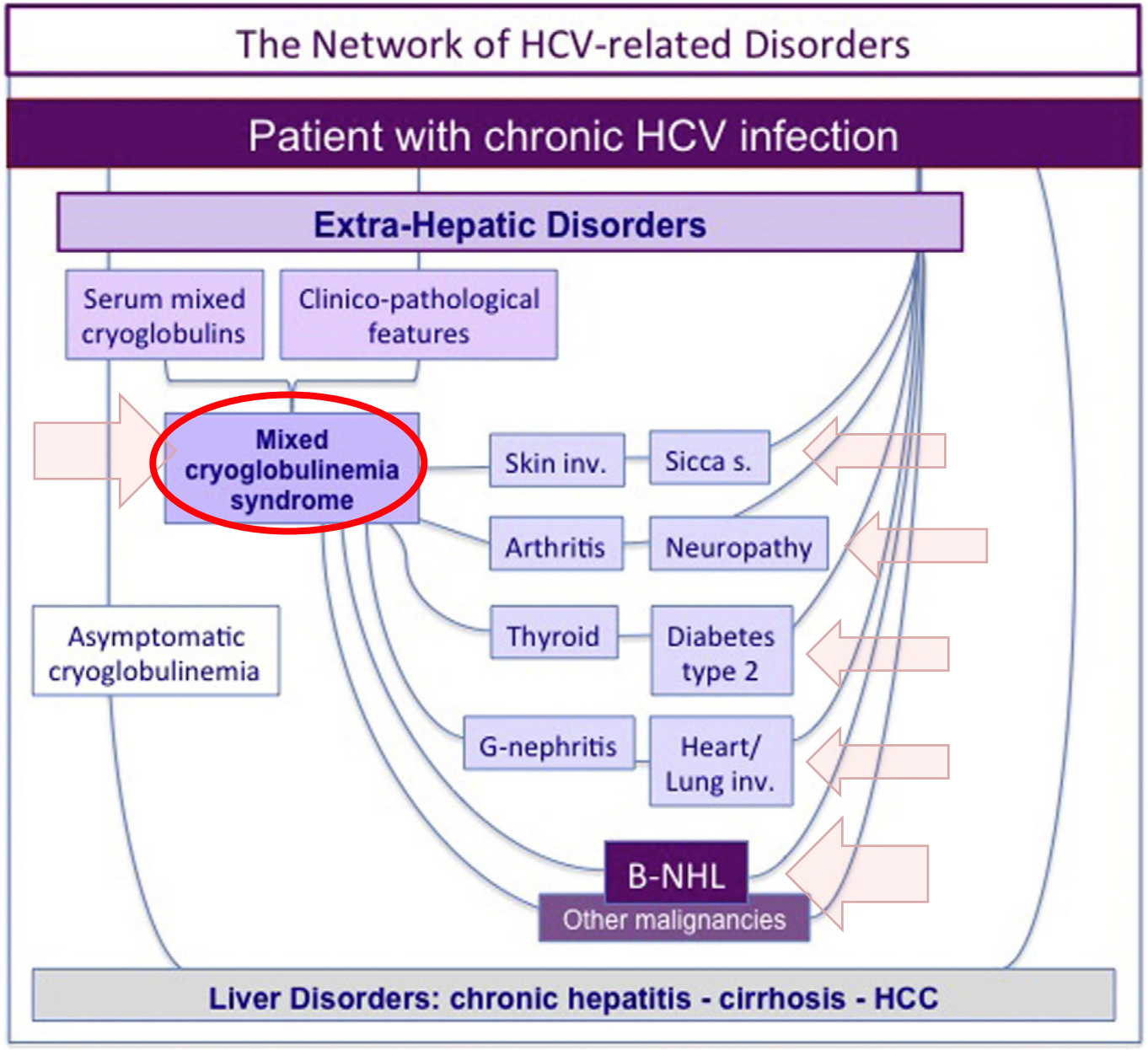


Mixed Cryoglobulinemia a crossing road autoimmunity/linphoproliferation/cancer

2016

International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement

Ferri C. et al. Autoimmunity Rev 2016



Autoimmunity Reviews 15 (2016) 1145–1160

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement

Clodoveo Ferri [a,*], Manuel Ramos-Casals [b], Anna Linda Zignego [c], Luca Arcaini [d,e], Dario Roccatello [f], Alessandro Antonelli [g], David Saadoun [m,n,o,p], Anne Claire Desbois [m,n,o,p], Marco Sebastiani [a], Milvia Casato [h], Peter Lamprecht [i], Alessandra Mangia [j], Athanasios G Tzioufas [k], Zobair M Younossi [l], Patrice Cacoub [m,n,o,p], on behalf of the ISG-EHCV coauthors [1]

Fig. 2. The network of HCV-related disorders. The figure is a schematic representation of the network of HCV-related disorders, which encompasses both hepatic and extrahepatic diseases (HCV-EHDs; see also Table 2). Liver involvement represents the most common clinical manifestation of chronic HCV infection, while HCV-EHDs may develop in a subgroup of patients. HCV-EHDs may appear either as organ-specific disorders, i.e. arthritis, neuropathy, glomerulonephritis, etc.) or as systemic auto-immune disorder such as mixed cryoglobulinemia syndrome (MCS). Isolated and totally asymptomatic serum cryoglobulins are generally detectable in over 50% of HCV infected individuals, while classical MCS can be diagnosed in 15% of cryoglobulin-positive patients on the basis of both serological (circulating mixed cryoglobulins) and typical clinic-pathological features (see text). In clinical practice, we can observe a variable combination of hepatic and HCV-EHDs among HCV-infected patients, as well as in the same patient during the long-term follow-up. The most harmful complications of chronic HCV infection may appear abruptly (sensory-motor peripheral neuropathy, glomerulonephritis, widespread vasculitis, etc.) or more often as late manifestations (malignancies), alone or in the setting of MCS. B-NHL: B-cell non-Hodgkin's lymphomas; HCC: hepatocellular carcinoma.

2021

The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

CORRESPONDENCE

Extrahepatic Manifestations of Chronic HCV Infection

Published June 30, 2021 | N Engl J Med 2021;385:94-96 | DOI: 10.1056/NEJMc2106143 | VOL. 385 NO. 1
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HCV in Autoimmunity & Oncogenesis

Extrahepatic Manifestations of Chronic HCV Infection

TO THE EDITOR: In their recent review article, Cacoub and Saadoun (March 18 issue)[1] do not sufficiently highlight our pioneering research that led to the current definition of extrahepatic manifestations of hepatitis C virus (HCV) infection. A description of these pivotal studies might have provided beneficial insights.

In those studies, we found a striking association between HCV and mixed cryoglobulinemia syndrome, and the studies also showed the lymphotropism of HCV.[2-4] Mixed cryoglobulinemia syndrome is a multifaceted disorder that mimics most extrahepatic manifestations of HCV infection,[2,4] and chronic HCV infection may trigger multiple pathogenetic alterations that are responsible for autoreactive, lymphoproliferative, and neoplastic disorders. HCV infection may exert an oncogenic role in B-cell non-Hodgkin's lymphomas as well as in hepatocellular carcinoma.[5,6]

The different phenotypes of extrahepatic manifestations of HCV infection may be the consequence of multistep and multifactorial pathogenetic processes. Both environmental and genetic cofactors may alter the disease progression from asymptomatic HCV infection to the most severe complications.

Clodoveo Ferri, M.D.

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University of Florence
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No potential conflict of interest relevant to this letter was reported.

1. Cacoub P, Saadoun D. Extrahepatic manifestations of chronic HCV infection. N Engl J Med 2021;384:1038-52.
2. Ferri C, Greco F, Longombardo G, et al. Association between hepatitis C virus and mixed cryoglobulinemia [see comment]. Clin Exp Rheumatol 1991;9:621-4.
3. Zignego AL, Macchia D, Monti M, et al. Infection of peripheral mononuclear blood cells by hepatitis C virus. J Hepatol 1992; 15:382-6.
4. Ferri C, Monti M, La Civita L, et al. Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. Blood 1993;82:3701-4.
5. Ferri C, Caracciolo F, Zignego AL, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br J Haematol 1994;88:392-4.
6. Ferri C, Pileri S, Zignego AL. Hepatitis C virus, B-cell disorders, and non-Hodgkin's lymphoma. In: Goedert JJ, ed. Infectious causes of cancer: targets for intervention. Totowa, NJ: Humana Press, 2000:349-68.

DOI: 10.1056/NEJMc2106143

Homage to pre-socratic philosopher-scientists

...neither philosophers, nor scientists

2022

Autoimmunity Reviews

Volume 21, Issue 1,
January 2022

https://doi.org/10.1016/j.autrev.2021.102923Get rights and content

Effects of antiviral therapies in patients with HCV-related Cryoglobulinemic Vasculitis

Predictors of long-term cryoglobulinemic vasculitis outcomes after HCV eradication with direct-acting antivirals in the real-life

Laura Gragnani [a], Serena Lorini [a], Silvia Marri [a], Caterina Vacchi [b], Francesco Madia [a], Monica Monti [a], Clodoveo Ferri [c 1], Anna Linda Zignego [a 1]

Abstract

Cryoglobulinemic vasculitis (CV) is the most frequent extrahepatic manifestation during HCV-chronic infection. An effective Direct Acting Antiviral-treatment leads to CV clinical response in the majority of CV-patients although symptoms may persist/recur despite a sustained virological response. At present, no standardized clinical predictive factorsfor disease maintenance/recurrence were proposed, as emerged from a complete literature review we performed and reported.
Here we provided a detailed descriptive analysis of a wide population of CV patients treated with DAA-based regimes and followed-up after therapy completion for longer than 72 weeks, in order to identify clinical or laboratory predictors of disease outcome and to optimize the patient management.
Together with some baseline symptoms (neuropathy, weakness and sicca syndrome), two newly created scores, CV- and Global Severity Index, emerged as reliable and standardized tools to predict CV clinical response before initiating an antiviral therapy. In addition to predictive parameters previously proposed in the world literature, these novel Indexes could fill an unmet gap in the clinical management of the complex HCV-related CV.

2022

Journal of Clinical Immunology

Impact of COVID19 pandemic on patients with MC syndrome

Journal of Clinical Immunology
https://doi.org/10.1007/s10875-023-01444-4

ORIGINAL ARTICLE

Check for updates

COVID-19 and Mixed Cryoglobulinemia Syndrome: Long-Term Survey Study on the Prevalence and Outcome, Vaccine Safety, and Immunogenicity

Laura Gragnani[1] · Marcella Visentini[2] · Serena Lorini[1] · Stefano Angelo Santini[3,4] · Gianfranco Lauletta[5] · Cesare Mazzaro[6] · Teresa Urraro[7] · Luca Quartuccio[8] · Fabio Cacciapaglia[9] · Piero Ruscitti[10] · Antonio Tavoni[11] · Silvia Marri[1] · Giuseppina Cusano[2] · Luisa Petraccia[1] · Caterina Naclerio[7] · Elena Treppo[8] · Giulia del Frate[8] · Ilenia Di Cola[10] · Vincenzo Raimondo[12] · Daniela Scorpiniti[12] · Monica Monti[1] · Lorenzo Puccetti[11] · Giusy Elia[13] · Poupak Fallahi[14] · Stefania Basili[2] · Salvatore Scarpato[7] · Florenzo Iannone[9] · Milvia Casato[2] · Alessandro Antonelli[13] · Anna Linda Zignego[1] · Clodoveo Ferri[15,12]

the scientific community recognizes and expands the results of researches

masks

Lacture
HCV-MC & B-NHL

IMMUNOVASCULITIS
from Molecular Pathology
to Specific Therapy

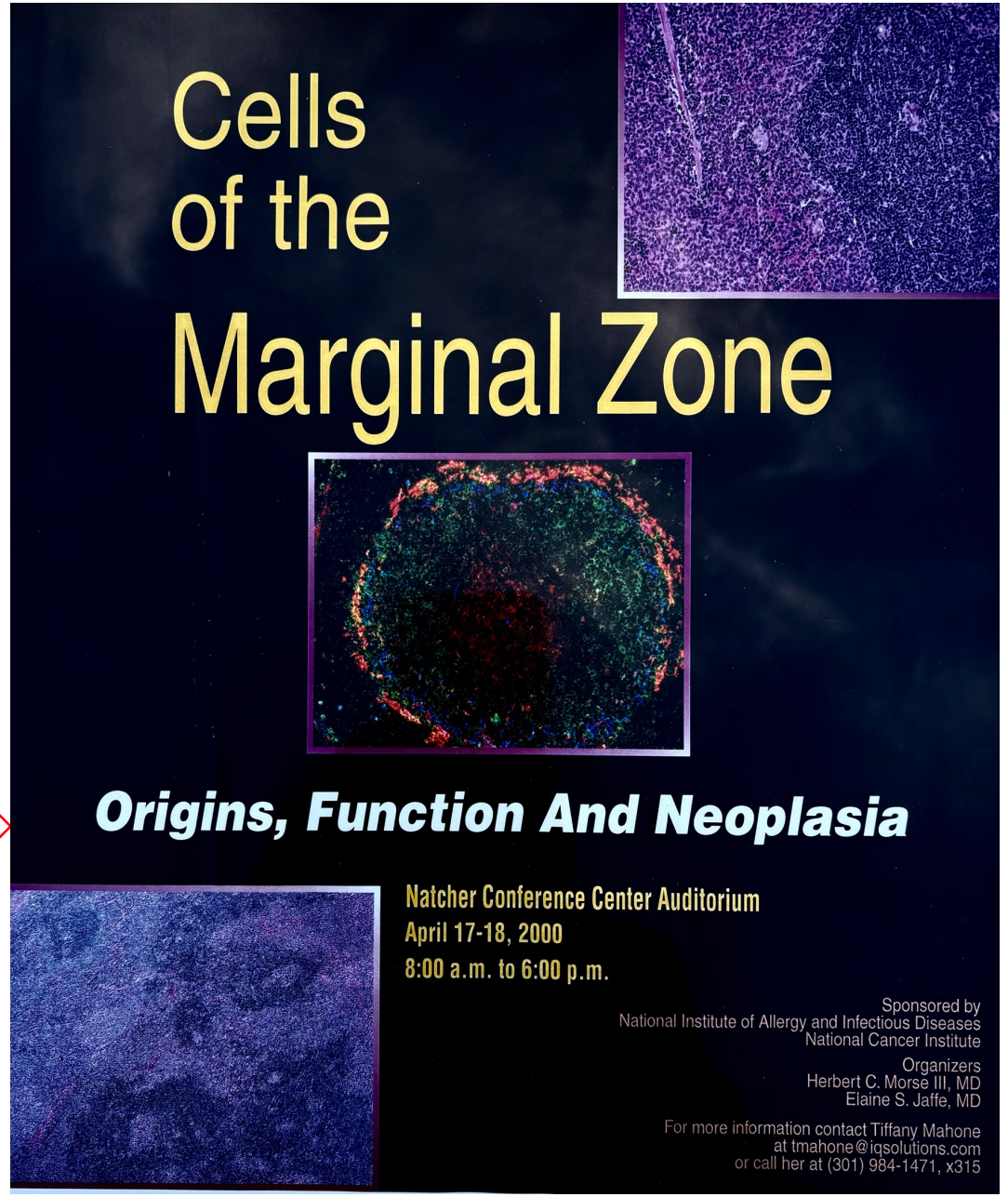
Hamburg 2000, Germany

International Meeting of Experts
of Systemic Vasculitides
Churg J, Agnello V, Ferri C,
Calabrese LH, Jannette JC,
Savage C, Gross W

Lacture
HCV infection & B-NHL

Congress on
Cell of the Marginal Zone

National Institute of Allergy & Infectious Diseases
National Cancer Institute
Bethesda MD, USA
April 2000

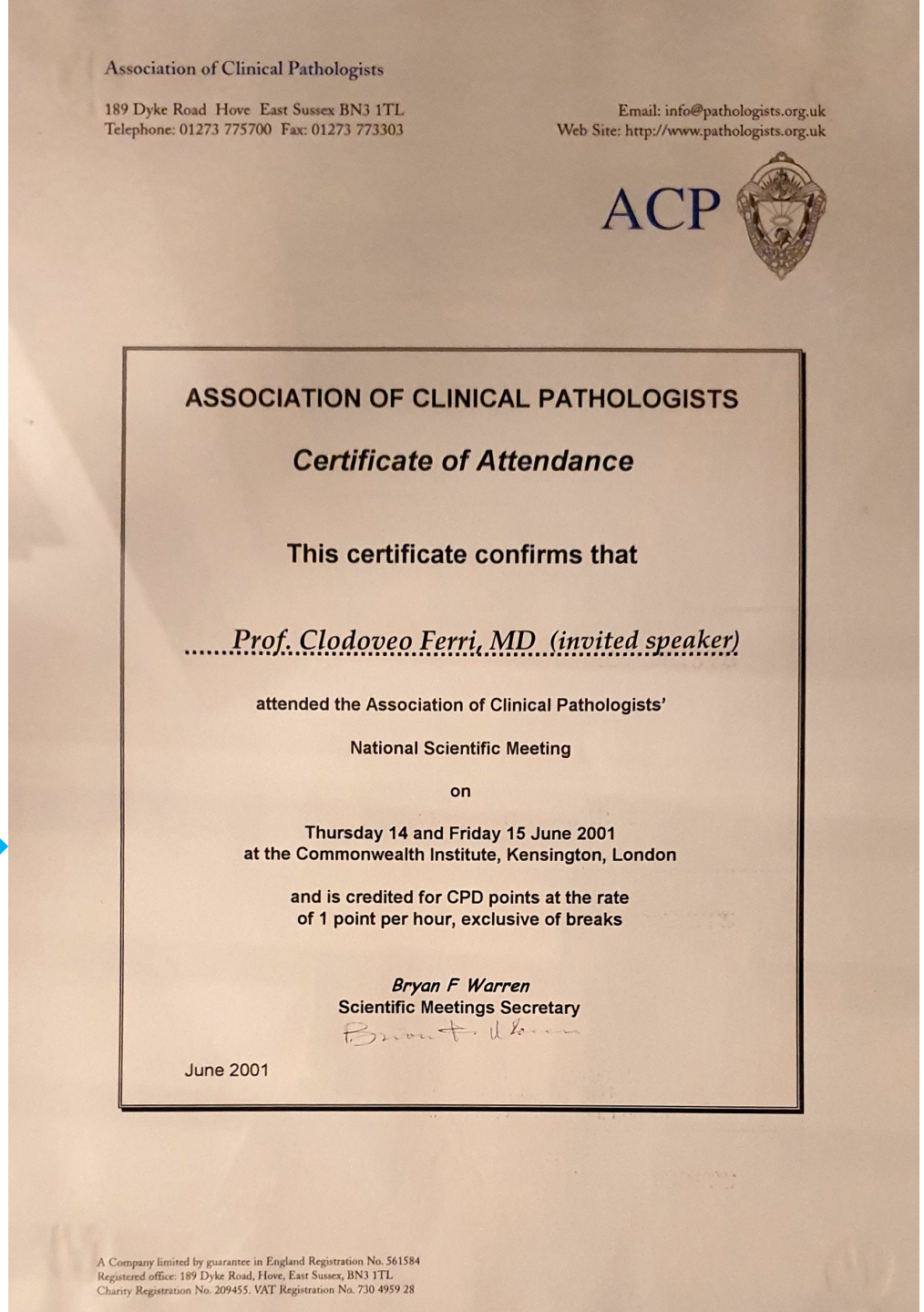


2001

Lecture
HCV-MC & B-NHL

Association of Clinical Pathologists
National Scientific Meeting

London UK



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ACP

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Certificate of Attendance

This certificate confirms that

Prof. Clodoveo Ferri, MD (invited speaker)

attended the Association of Clinical Pathologists'

National Scientific Meeting

on

Thursday 14 and Friday 15 June 2001
at the Commonwealth Institute, Kensington, London

and is credited for CPD points at the rate
of 1 point per hour, exclusive of breaks

Bryan F Warren
Scientific Meetings Secretary

June 2001

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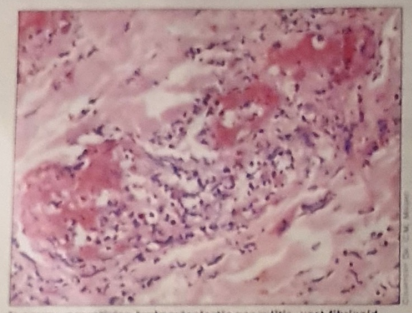
Clodoveo Ferri
Overview of the Research Line: from Mixed Cryoglobulinemia (Cryoglobulinemic Vasculitis) to HCV infection, Autoimmunity, and Oncogenesis.
1972 -2024

2006

Rheumatology News
www.rheumatologynews.com
Vol. 5, No. 4 — The Independent Newspaper for the Rheumatologist — April 2006



In severe necrotizing leukocytoclastic vasculitis, vast fibrinoid necrosis of the vessel wall and permeation by neutrophils occur.

HCV: Key Target of Vasculitis Therapy

BY NANCY WALSH
New York Bureau

ABANO TERME, ITALY — The finding that the hepatitis C virus is implicated in the pathogenesis of cryoglobulinemic vasculitis means that therapy must address the chronic viral infection, the autoimmune dysregulation, and the potential for associated lymphoproliferative disorders, Dr. Clodoveo Ferri said at a congress on skin, rheumatism, and autoimmunity.

A linkage between hepatotropic viruses and cryoglobulinemia has been suspected for 3 decades, but only when hepatitis C virus (HCV) was identified was the causative connection made. In 1991, Dr. Ferri and his colleagues found a "striking correlation" among patients with mixed cryoglobulinemia and HCV seropositivity and also with hepatitis C viremia (Clin. Exp. Rheumatol. 1991;9:621-4). In Italy today, 95% of cases of cryoglobulinemia are HCV related, said Dr. Ferri, chair of the rheumatology department, University of Modena e Reggio Emilia Medical School, Italy.

The condition formerly termed "essential" mixed cryoglobulinemia is a leukocytoclastic vasculitis of small- and medium-sized vessels that manifests clinically with purpura, weakness, and arthralgias. Circulating mixed polyclonal IgG and monoor polyclonal IgM immunoglobulins are present, rheumatoid factor typically is positive, and C4 is low. Organ involvement results from deposition of immune complexes and complement.

The interplay between HCV infection and immune system abnormality is complex and may relate to a molecular mimicry mechanism involving certain HCV antigens and host autoantigens, with the result being B-lymphocyte activation and proliferation and autoantibody production (Curr. Opin. Rheumatol. 2006;18:54-63).

See **Vasculitis** *page 16*

INSIDE

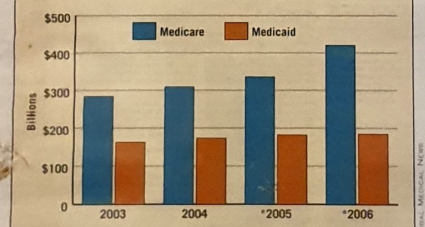
Manifestations of Asherson's
Tissue necrosis is a classic symptom of the disease.
PAGE 6

Dr. Dean Ornish: WHI Concerns
Low-fat diets could be harder to recommend.
PAGE 10

Preventing Rickets
Fortified milk may help fend off infant osteopenia.
PAGE 11

VITAL SIGNS

Medicare Spending to Increase by 25% in 2006



*Estimated costs.
Source: Health Affairs 2006;25:w61-w73

Risks of Hormones Trump Benefits for Bones, WHI Finds

Protection seen for hip, vertebral fractures.

BY MITCHEL L. ZOLER
Philadelphia Bureau

BETHESDA, MD. — The looming irony surrounding the hormone therapy study of the Women's Health Initiative was how wrong most experts had been about the potential benefits of estrogen in postmenopausal women.

Before the study, some had questioned the ethics of running a hormone-therapy trial with a placebo arm. But almost 4 years after the early halt to the estrogen-plus-progestin arm of the Women's Health Initiative (WHI), the final-outcomes balance sheet shows many risks and few benefits. The second, estrogen-only arm of WHI ran a little longer and compiled better results, with the risks of treatment roughly equaling its benefits. But the bottom line for both forms of hormone therapy is that they are now recommended only for select clinical situations.

The major benefits were a reduction in hip and clinical vertebral fractions with both the estrogen-plus-progestin and the estrogen-only, and a reduction in the rate of invasive colorectal cancer in patients treated with estrogen plus progestin, said Dr. Marcia L. Stefanick, professor of medicine at Stanford (Calif.) University, speaking at a 2-day conference at the National Institutes

See **Benefits for Bones** *page 21*

Natalizumab Indication for Rheumatoid Arthritis: No Go

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. — The return of natalizumab to the market will not extend to its use in management of rheumatoid arthritis, according to a spokesperson for its manufacturer Biogen Idec.

The company has dropped its plans to pursue Food and Drug Administration approval of an indication for use of natalizumab (Tysabri) in the management of rheumatoid arthritis, the spokesperson said in an interview. At its meeting last month, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee recommended that natalizumab's return to the market for treating patients with relapsing forms of multiple sclerosis with the protective measure of having mandatory risk minimization plan in place to enhance clinical vigilance for early signs of progressive multifocal leukoencephalopathy.

The drug was taken off the market in February 2005 and ongoing trials in MS, rheumatoid arthritis, and Crohn's disease

See **Natalizumab** *page 24*

From Prof. R Heimann,
anatomo-pathologist,
President Eur. Soc. Pathology,

back in 1971 he had observed at autopsy the **coexistence of lymphoma and cirrhosis,** the first disease was responsible for the patient's death, while the second one was not attributable to known causes.
This concomitance suggested a common causal factor.
Only after twenty years, the **discovery of HCV** and its link with known diseases (MC, cirrhosis, and B-NHL) **confirmed the previously supposed etiopathogenetic link:**

Limphoproliferation
Liver cirrhosis
Viral infection

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Docteur N. RENARD

Professor Clodoveo Ferri
Istituto Patologia Medica 1
University of Pisa
Pisa,Italy.

Dear Professor Ferri:

A colleague of mine drew my attention some months ago to the letter which you wrote to the J A M A and which appeared in August 1994.

Actually I am familiar with your previous work on mixed cryoglobulinemia and HCV but this letter delighted us specially because it backs up the concept of a link between viral hepatitis and some maligant lymphoproliferative disorders,concept which we put forward more than 20 years ago !.

In the meantime, a paper by Galun et al.appeared in the American Journal of Pathology involving HBV;this paper prompted us to write a letter to the editor of the Am.J.Pathol.

I enclose a copy of that letter and also a xerox of an old naive paper,the first one,which we wrote on that topic because I think it might amuse you.

With my best regards.

Sincerely yours.

Pr.R.Heimann.

SOCIETAS EUROPÆA PATHOLOGORUM

EUROPEAN SOCIETY OF PATHOLOGY

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Tel : xx 32-2-477 5081
Fax : xx 32-2-477 5085

5 February 1997

Professor Clodoveo Ferri
Istituto de Patologia Medica 1
Universita of Pisa
Via Roma 67
5600 Pisa. Italia
Fax :00 39 50 550582

553 638

Dear Professor Ferri

Many thanks for your letter dated January 3. I really enjoyed reading your recent publications.
I am also very impressed by the tremendous activity of your group.

You have no idea how pleased I am to find beautifully demonstrated in a modern and sophisticated way, the hypothesis which we crudely ventured more than twenty years ago.
Anecdotally, I remember the kind words which an oncologist at the Cancer Institute, seated behind me during a CPC, whispered in my ear : « Heimann, avec tes cirrhoses et lymphomes, tu racontes des conneries ! »
I am also impressed by the fact that the concept that some lymphoproliferative disorders could be related to Hepatitis C has been developped essentially if not exclusively in Italy .

I just came back from a haematopathology course in San Diego, California where among others, I met Nancy Harris , one of the teachers and who is a well known haematopathologist at the Mass. General Hospital in Boston. I know her for many years. She was aware of our respective works and as matter of fact she alludes to the paper of Pozzato et al.(Blood 1994) in her chapter on low grade B-cell lymphomas in the recent (1996) monography on pathology of the lymphnodes edited by Lawrence Weiss and published by Churchill Livingstone .
So slowly but surely the concept that hepatitis viruses can induce lymphoproliferative disorders is gaining acceptance in the haematopathologists' community !

I thank you very much also for the offer to collaborate with you. Actually, I was chairman of the Department of Pathology at the Institut Jules Bordet until my retirement in October 1995 ; I am now consultant at the Department of Pathology of the Flemish Medical School and Academic Hospital ; I shall hold this full-time position until end of March and from then on, I shall remain consultant on a part-time basis. So I shall have plenty of time then . I would be delighted to collaborate with your team and would like to discuss with you how this could be done. Maybe we could meet for instance sometime in this coming spring or early summer at your best convenience ?.
In fact,my wife and I had planned to drive down to Rome and visit some close friends there.The date is still open and I would not mind taking the opportunity to visit you in Pisa. If you wish, I could even give a talk on the historical steps of our understanding of the relashionship between liver diseases and lymphoproliferative disorders.

Looking forward to hearing from you and with my best regards, I am ,

Yours sincerely.

R.Heimann

P.S. I did not succeed in sending you this letter in a fax.

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Letters from Prof. R Heimann,
anatomo-pathologist, President Eur. Soc. Pathology,

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I just came back from a haematopathology course in San Diego, California where among others, I met Nancy Harris , one of the teachers and who is a well known haematopathologist at the Mass. General Hospital in Boston. I know her for many years. She was aware of our respective works and as matter of fact she alludes to the paper of Pozzato et al.(Blood 1994) in her chapter on low grade B-cell lymphomas in the recent (1996) monography on pathology of the lymphnodes edited by Lawrence Weiss and published by Churchill Livingstone .
So slowly but surely the concept that hepatitis viruses can induce lymphoproliferative disorders is gaining acceptance in the haematopathologists' community !

I thank you very much also for the offer to collaborate with you. Actually, I was chairman of the Department of Pathology at the Institut Jules Bordet until my retirement in October 1995 ; I am now consultant at the Department of Pathology of the Flemish Medical School and Academic Hospital ; I shall hold this full-time position until end of March and from then on, I shall remain consultant on a part-time basis. So I shall have plenty of time then . I would be delighted to collaborate with your team and would like to discuss with you how this could be done. Maybe we could meet for instance sometime in this coming spring or early summer at your best convenience ?.
In fact,my wife and I had planned to drive down to Rome and visit some close friends there.The date is still open and I would not mind taking the opportunity to visit you in Pisa. If you wish, I could even give a talk on the historical steps of our understanding of the relashionship between liver diseases and lymphoproliferative disorders.

Looking forward to hearing from you and with my best regards, I am ,

Yours sincerely.

R.Heimann

PS. I did not succeed in sending you this letter in a fax.

1996
Haematologica
Editorial

HEPATIS C VIRUS: A LINKAGE BETWEEN HEMATOLOGY AND HEPATOLOGY ESTABLISHED THROUGH MAJOR CONTRIBUTIONS BY ITALIAN RESEARCH

editorial
Haematologica 1996; 81:193-194

HEPATIS C VIRUS: A LINKAGE BETWEEN HEMATOLOGY AND HEPATOLOGY ESTABLISHED THROUGH MAJOR CONTRIBUTIONS BY ITALIAN RESEARCH

In this issue of Haematologica, Luppi and Torelli analyze the pathogenetic role of some lymphotropic viruses in human lymphoproliferative disorders.[1] This has been a field of active research in the last few years, and we should be proud of the fact that important investigations on the relationship between hepatitis C virus (HCV) and lymphoproliferative disorders have been performed in Italy. In addition, Torelli and coworkers have made important contributions to studies on herpesviruses.

The close association between HCV infection and mixed cryoglobulinemia (MC) represented the first evidence that this virus may have an etiopathogenetic role in lymphoproliferative disorders. Ferri *et al.*[2] investigated the prevalence of HCV infection of peripheral blood mononuclear cells in a series of 16 patients with type II mixed cryoglobulinemia. Previous exposure to HCV was shown in all cases (100%); moreover, HCV RNA was detected in peripheral lymphocytes from 13 out of the 16 patients, whereas it was never found in mononuclear blood cells from 20 control subjects. These findings strongly suggested that HCV infection might be responsible for the clonal B-cell expansion underlying the systemic manifestations of MC.

Pozzato *et al.*[3] studied the clinical, histologic, and virologic findings of 31 patients affected with mixed cryoglobulinemia. The prevalence of anti-HCV antibodies was high (84%); polymerase chain reaction amplification of the 5' untranslated region of HCV was positive in 84% of subjects, and core region amplification was positive in 96%. A high prevalence of genotype II was found (77%), and chronic liver disease was present in 48% of patients. Bone marrow biopsy specimens showed the presence of low-grade non-Hodgkin's lymphomas in 12 cases (39%), whereas infiltration appeared to be reactive rather than monoclonal in 11 patients. This study confirmed that mixed cryoglobulinemia is closely associated with HCV infection since only one patient was apparently not infected by the virus, and suggested that this disease is associated with a high prevalence of low-grade non-Hodgkin's lymphomas (NHLs).

The same authors investigated the long-term effects of α-interferon on clinical, hematological and virological parameters in a group of 18 patients affected with type II mixed cryoglobulinemia.[4] A bone marrow biopsy was performed in all patients, and a liver biopsy was obtained in those with biochemical signs of chronic liver disease. All patients followed the same treatment schedule: three million units of recombinant interferon-α s.c., three times a week for 1 year. In 5 cases bone marrow histology showed the presence of a monoclonal lymphocytic infiltrate. Liver biopsies were performed in 13 (72%) of the patients and chronic liver disease was found in all 13. Anti-HCV antibodies were present in 17 (95%) subjects. HCV-RNA was detected in all cases (100%) before therapy. Five (28%) patients achieved a complete response and 9 (50%) a partial response, while the others (4 cases, 22%) showed minor responses. Four patients cleared the virus and obtained a complete remission of the MC. This study confirmed that HCV may be a cause of mixed cryoglobulinemia and suggested that α-interferon may be an effective agent for the treatment of this disorder.

At this point Ferri *et al.* decided to investigate HCV infection in a series of 50 unselected Italian patients with B-cell NHL.[5] Antibodies against HCV were found in 30% of NHL, and HCV viremia in 32% of cases. HCV-related markers were detected in 34% (17/50) of NHL patients; this prevalence is particularly significant when compared with HCV seropositivity in Hodgkin's disease (3%) and healthy controls (1.3%). These data have been confirmed by Cavanna *et al.*[6]

Franzin *et al.*[7] investigated clonal expansions of IgM-producing B cells in 38 patients with a chronic hepatitis C virus infection. Eight patients were affected with type II mixed cryoglobulinemia (two of whom also suffered from non-Hodgkin's lymphoma and one from Waldenström's disease), one with type III mixed cryoglobulinemia, one with Waldenström's disease, and 28 with chronic liver disease. Clonal Ig gene rearrangements were detected in all patients with type II mixed cryoglobulinemia, as well as at a high frequency (24%) in the HCV-infected patients without cryoglobulinemia. A polyclonal pattern was present in the patient with type III mixed cryoglobulinemia and in the 15 normal individuals and 16 age-related patients with HCV-negative alcoholic liver disease investigated as controls. The serum levels of rheumatoid factor were increased in all patients with a clonal expansion, suggesting that the expanded B-cell clones belong to the rheumatoid factor-producing B-cell subset.

De Vita *et al.* have reported for the first time localization of HCV within a parotid non-Hodgkin's lymphoma (NHL) lesion in the course of HCV-related type II essential MC, an important step toward implicating this agent in lymphomagenesis.[8] Plus and minus strand HCV RNA was first demonstrated by polymerase chain reaction on complete RNA from the lesion. Sialotropic viruses already shown to be involved in lymphoproliferation, ie Epstein-Barr virus and human herpesvirus-6, were absent from the same tissue lesion. According to the current models of B-cell lymphomagenesis, a role for HCV as an exogenous antigenic stimulus should be considered for NHL development in the present case, whereas malignant B cells do not seem to permit active HCV replication.

These are just a few examples of the major contributions made by Italian science toward defining the pathogenetic role of HCV in lymphoproliferative disorders. The reader is referred to the review by Luppi and Torelli[1] for details.

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Naca

1992

After the first demonstration of the association HCV-MC (1991)

ABSTRACTISSIME 92

Les Best d'Abstract Rhumato (p. 7).

ABSTRACT
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Quatre-vingt-treize.
Est-ce une révolte décrite par une plume hugolienne ? Non, lecteurs, c'est une révolution (terrestre !). La prochaine.
Abstract Rhumato s'y prépare, jetant ses troupes les plus valeureuses dans le dernier combat de 1992, le quatre-vingt-quatorzième depuis qu'il va au feu.
Clodoveo Ferri a été désigné pour partir en éclaireur. On ne pouvait mieux choisir que ce condottiere pisan pour débusquer le virus de l'hépatite C camouflé dans le maquis des cryoglobulinémies (Le Lauréat, page 5).
Mais voici en seconde ligne les meilleurs du bataillon d'articles, de ceux qu'on distingue et qu'on décore de lauriers pour avoir au milieu de tant d'autres papiers mené la charge d'Abstract Rhumato pendant toute cette année que nous disions presque révolue (Les Best, page 7).
Mais où en sont les alliés ?
C'est-à-dire les rhumatologues du reste de l'Europe... Qu'on ne s'y trompe pas ! Ici ou de l'autre côté des ci-devant frontières, c'est le même combat (Rhumato sans frontières, page 14).
Plus loin, les autres corps d'armée (cardiologues, neurologues, psychiatres, gastro-entérologues, pédiatres, dermatologues, gynécologues...) se sont réunis pour parler de la stratégie de leurs propres combats.
Faites circuler le mot de passe (Médicoscopie, page 22)...
Cependant, les négociations se poursuivent à l'arrière. Vérifiant plus que jamais l'adage "la guerre est décidée par ceux qui ne la font pas", ministres de la santé, directeurs de caisse et présidents des syndicats professionnels en sont encore aux Grandes Manœuvres malgré plusieurs plans de batailles successivement avalisés puis rejetés.
Il n'y aura pas en 92 de Convention nationale... nonobstant les accords historiques (Profession santé, page 27).
Bref, il n'est que temps de nous accorder une trêve. Celle de Noël par exemple.

Marie-Line Barbet

Si ces résultats se trouvent confirmés, le nombre des CGM dites essentielles devrait donc singulièrement diminuer. Reste que les mécanismes physiopathologiques qui pourraient expliquer la relation entre VHC et CGME ne sont pas encore totalement éclaircis. Selon notre chercheur italien *"le VHC, mais également à un moindre degré le VHB ou d'autres virus inconnus, pourrait provoquer un trouble lymphoprolifératif responsable de la production de facteur rhumatoïde et de taux élevés de complexes immuns circulants (CIC) incluant les cryoglobulines, ces dernières étant responsables de lésions vasculaires à l'origine des différentes manifestations cliniques"*. De plus, *"une altération de la clairance des CIC par les cellules de Küppfer peut contribuer à maintenir des taux sériques élevés de cryoglobulines potentiellement toxiques"*.

Pour l'instant il est cependant impossible à C. Ferri de confirmer la possible séquence : infection par le VHC - hépatite chronique - cryoglobulinémie. Mais il précise cependant que *"le suivi de plus de 200 cas de CGM montre que pour 20 % des dossiers, l'hépatite précède les manifestations typiques de la CGM (purpura, asthénie, arthralgies, neuropathie périphérique, néphropathie, ulcérations cutanées). Dans 48 % des observations, l'hépatite apparaît au cours de l'évolution de la maladie alors que dans 32 % des cas, une atteinte clinique hépatique manifeste n'est pas détectable ; la prévalence du VHC étant dans ce dernier cas comparable à celle observée pour la totalité des CGM"*.

Cependant la plupart des études réalisées incluaient de nombreux patients porteurs d'anomalies hépatiques. Y aurait-il là un biais ? Apparemment pas pour notre rhumatologue pisan qui avance que *"la même prévalence des marqueurs du VHC constatée dans le groupe des patients n'ayant aucun signe clinique ni sérologique d'hépatite indique clairement que le VHC, qui est un virus à la fois hépatotrope et lymphotrope, est responsable de perturbations immunologiques plus complexes"*.

Plus encore, une fréquence élevée d'infection par le VHC ayant été rapportée dans les hépatites chroniques auto-immunes, C. Ferri et ses collaborateurs font l'hypothèse d'un mécanisme étiopathogénique commun aux CGM et aux hépatites chroniques auto-immunes.

Clodoveo Ferri, chercheur chaleureux pour une affection froide.

Un traitement à l'épreuve

Plusieurs équipes ont tenté de traiter les CGME par interféron (IFN) alpha avec un certain succès. C. Ferri propose cette modalité thérapeutique chez les patients ayant une infection à VHC manifeste et une maladie active, en général avec vascularite cutanée et hépatite.

De plus, il propose *"une personnalisation des modalités thérapeutiques, à savoir de la dose et de la durée du traitement, suivie par une diminution lente de l'IFN alpha afin d'éviter un phénomène de rebond, un critère d'exclusion important étant la présence d'une neuropathie périphérique sévère"*.

Les jours prochains seront donc encore laborieux pour ce clinicien infatigable, mais on peut l'espérer, riches en découvertes. Décidés à mieux cerner le rôle du VHC dans la CGM et les relations entre l'hépatite des CGM et l'hépatite chronique auto-immune, C. Ferri et son équipe aimeraient aussi étudier les possibilités d'évolution des CGM en lymphome malin et le rôle de l'infection par le VHC dans ce phénomène.

Patricia Thelliez

Gros plan sur les cryo

Les cryoglobulines (GC) sont des immunoglobulines qui précipitent au froid et se redissolvent à 37 °C.
On distingue :
- Des CG monoclonales (type I) qui sont formées d'un composant monoclonal, le plus souvent IgM.
- Des CG mixtes à composant monoclonal (type II) qui correspondent à des complexes immuns comprenant une immunoglobuline monoclonale (le plus souvent une IgM) et une immunoglobuline polyclonale, généralement une IgG, le premier constituant exerçant une activité rhumatoïde ou anti-idiotype contre le second.
- Des CG mixtes polyclonales (type III) constituées d'immunoglobulines polyclonales comprenant, le plus souvent, une IgM polyclonale à activité anti-IgG (facteur rhumatoïde).

Les CG de type I sont responsables des tableaux les plus sévères liés à l'hyperviscosité plasmatique et/ou à leur précipitation intravasculaire. Les CG mixtes, surtout de type II, provoquent une vascularite par dépôt de complexes immuns circulants avec classiquement asthénie, arthralgies, purpura et parfois anomalies hépatiques. Les CG mixtes de type III sont souvent asymptomatiques.

Les causes des CG sont multiples. Les CG monoclonales sont surtout observées au cours des lymphomes et des hémopathies. Les CG mixtes sont essentiellement constatées au cours d'affections auto-immunes ou infectieuses. Dans 18 à 30 % des cas, aucune cause ne peut être retenue : la CG est dite essentielle.

2000

Chapter textbook
Infectious Causes of Cancer

In collaboration with Prof.
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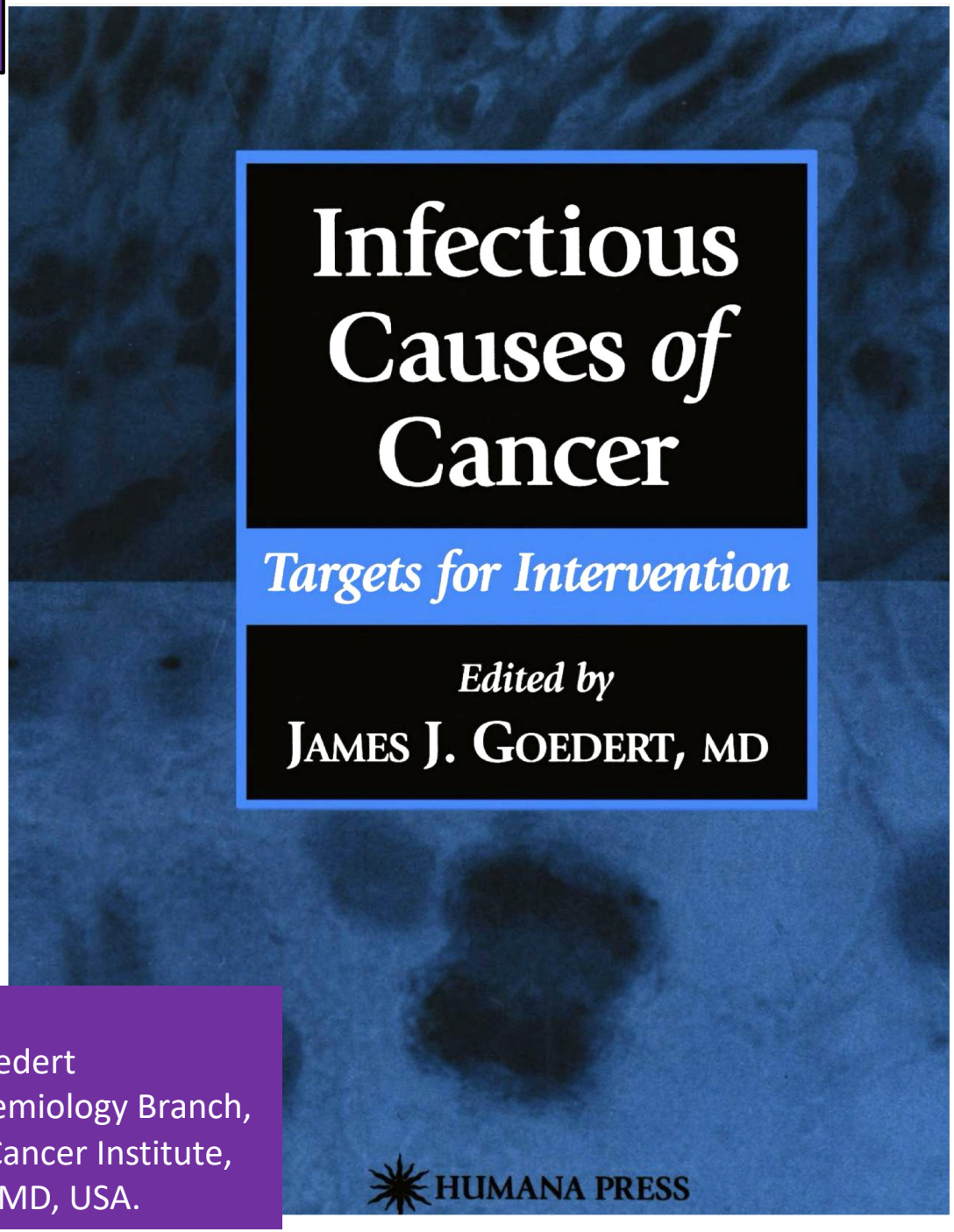
Anna Linda Zignego
internist
Univ. of Firenze



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Hepatitis C Virus, B-Cell Disorders, and Non-Hodgkin's Lymphoma

Clodoveo Ferri, Stefano Pileri, and Anna Linda Zignego

HEPATITIS C VIRUS INFECTION

Since its identification in 1989 *(1,2)*, hepatitis C virus (HCV) has been recognized as the major causative agent of posttransfusion and sporadic parenterally transmitted non-A–non-B hepatitis *(3)*. HCV is a single-stranded, positive-sense RNA virus showing similarities of genomic organization with pestiviruses. The introduction of second- and third-generation enzyme-linked immunosorbent assay (ELISA) and recombinant immunoblot assay (RIBA) tests significantly improved the diagnostic procedures for the detection of HCV-related antibodies (anti-HCV). Unlike many other viral infections, the detection of serum IgG class antibodies often suggests active HCV infection. However, anti-HCV may persist long after viral clearance. Thus, detection of viral RNA sequences using polymerase chain reaction (PCR) or other amplification methods is required to demonstrate infectous HCV *(4)*. In patients with non-A, non-B hepatitis there is generally a good concordance between anti-HCV and PCR results. The detection of HCV RNA sequences in tissue specimens by *in situ* hybridization could be usefully employed mainly for etiopathogenetic investigations, although this still requires proper validation *(5)*.

HCV genotypes have been defined by means of nucleotide and amino acid sequence analyses. There is an increasing number of HCV types and subtypes; at least 6 major HCV genotypes with 11 subtypes have been demonstrated in patient populations from different geographic areas *(6)*. The presence of different HCV genotypes seems to be relevant for both pathogenetic and therapeutic implications, as suggested by the increased prevalence of genotype 1b in subjects with low response to interferon treatment and genotype 2a/c in lymphoproliferative disorders *(3–8)*. Although some HCV genotypes are prevalent in particular geographic areas, a large variety of types and subtypes appears in a given country. In addition, HCV shows marked genetic variability. The viral genome is a mixture of heterogeneous HCV RNA molecules, often designated as quasispecies *(9)*. The coexistence of multiple mutants provides an efficient and rapid mechanism for the virus to escape the immune response and therefore to persist in the host. The large majority of infected individuals develop chronic HCV infection *(3,10)*, with about 70% showing chronic hepatitis.

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The Vasculitides

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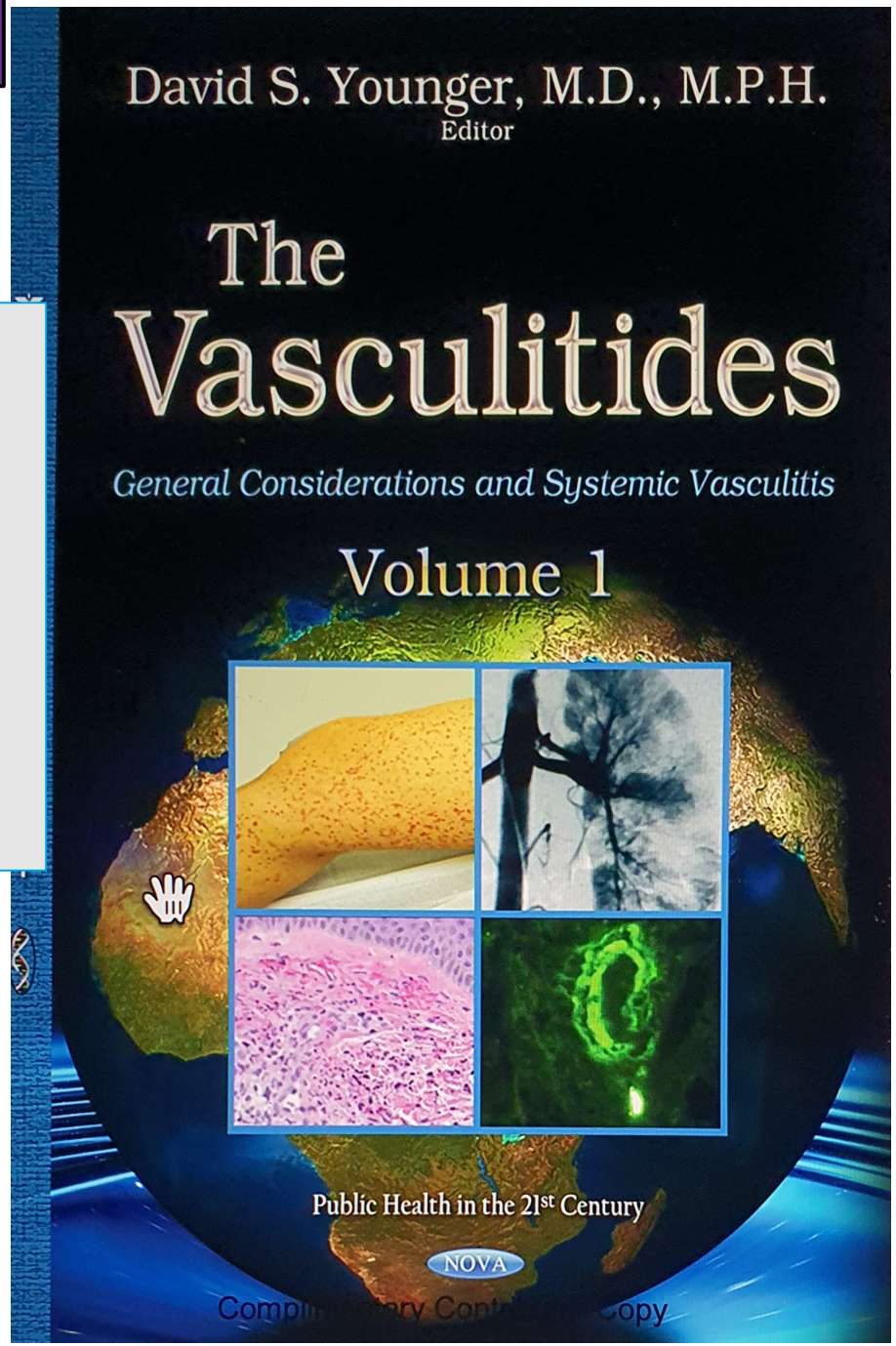

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Chapter 12

Cryoglobulinemic Vasculitis

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Abstract

Cryoglobulinemic vasculitis, also termed mixed cryoglobulinemic syndrome, is a rare systemic small vessel vasculitis due to the vascular deposition of immune-complexes, mainly mixed IgG-IgM cryoglobulins. It is associated with hepatitis C virus infection, immunological, and neoplastic diseases. Cryoglobulinemic vasculitis is characterized by the classical triad of purpura, weakness and arthralgia, frequent multiple organ involvement, and with infrequent late lymphatic and hepatic malignancies. The etiopathogenesis of cryoglobulinemic vasculitis is not completely understood. However, hepatitis C viral infection and associated lymphotropism, genetic and environmental factors play important roles in cryoglobulin and immune-complex production that deposit in blood vessels, and in B-lymphocyte expansion. The diagnosis is suggested by clinical evidence of purpura, circulating mixed cryoglobulinemia and low C4 levels, and pathologically evident leukocytoclastic vasculitis in skin biopsy lesions. The prognosis is poor in patients with renal disease, liver failure, and malignancy. Treatment is directed toward eradicating hepatitis C viral infection employing combination PEGylated-interferon-alpha and ribavirin treatment, immunomodulatory and immunosuppressant medications as warranted by the level of clinical severity.

Introduction

Cryoglobulinemic vasculitis (CV) is a small vessel vasculitis (SVV) due to the vascular deposition of cryoprecipitable or non-cryoprecipitable immune-complexes (IC) and complement [1]. Cryoglobulinemia and cryoimmunoglobulinemia are interchangeable terms

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Chapter
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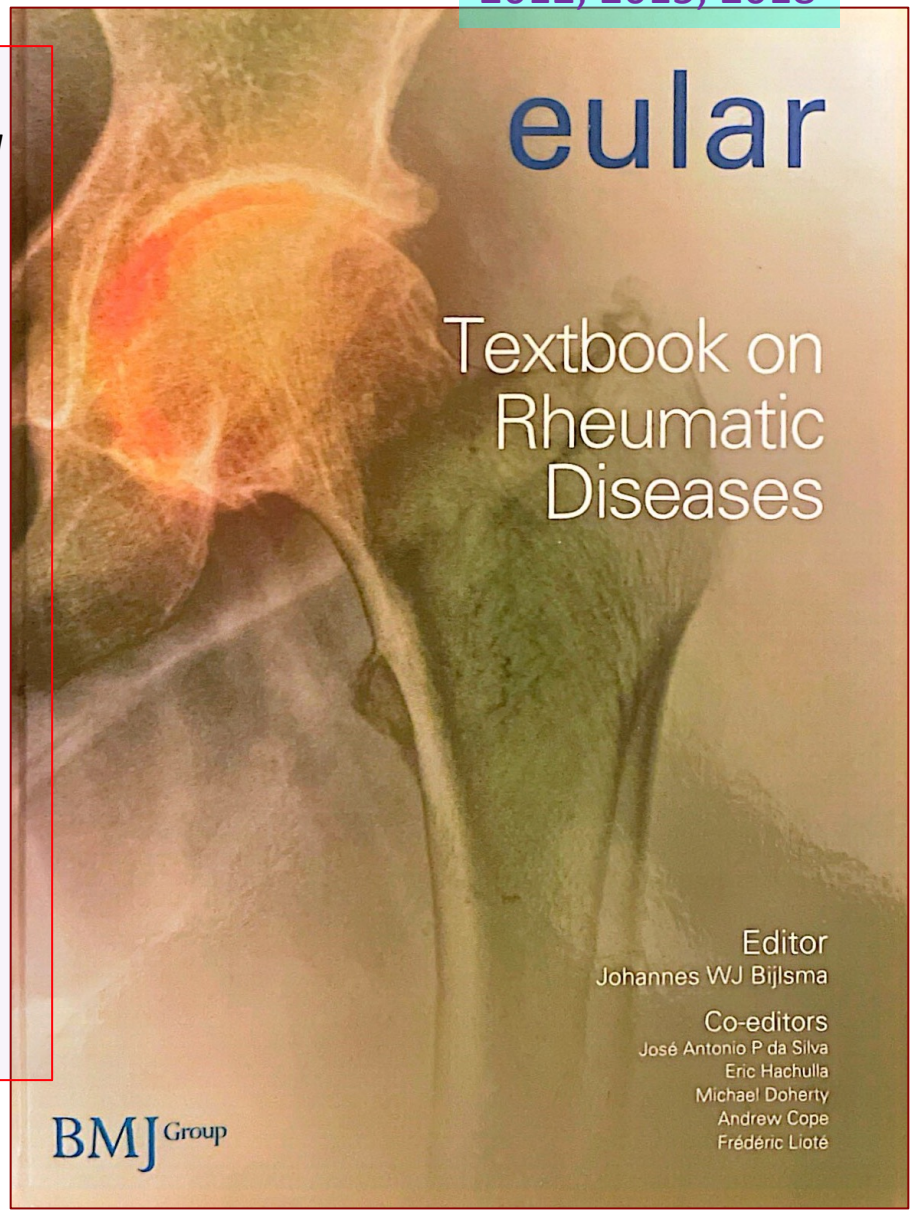

42 Cryoglobulinaemia and Hepatitis C Virus

Clodoveo Ferri, Marco Sebastiani, David Saadoun, Patrice Cacoub

A previous version was coauthored by Clodoveo Ferri, Maria Teresa Mascia, David Saadoun and Patrice Cacoub

Learning objectives:

- Correctly classify/diagnose cryoglobulinaemia and mixed cryoglobulinaemia (MC)
- Use the correct technical procedures to detect and characterise cryoglobulin
- Describe and explain the main mechanisms involved in the aetiopathogenesis of MC syndrome
- Outline the epidemiology, prognosis and main clinical manifestations of MC syndrome (cryoglobulinaemic vasculitis)
- Make a differential diagnosis between MC syndrome and other autoimmune rheumatic disorders (Sjögren's syndrome, rheumatoid arthritis, other systemic vasculitides)
- Define the main organ and systemic autoimmune disorders possibly triggered by hepatitis C virus (HCV) infection
- List the possible neoplastic complications correlated with HCV infection
- Describe and explain the pathogenetic mechanisms of HCV-related autoimmune and lymphoproliferative disorders
- List the main targets of HCV-mixed cryoglobulinaemia therapy: clinical response (organ target manifestations), virological response (HCV RNA) and immunological response (cryocrit, C4 serum level)
- Understand that antiviral therapy (Peg-interferon α plus ribavirin) is the cornerstone of HCV-mixed cryoglobulinaemia treatment
- Recognise that HCV viral load correlates with clinical outcome
- Know that B cell depleting therapy (rituximab) is an interesting additional therapeutic option
- Explain the timing of action and the limitations of rituximab
- Explain concerns about immunosuppressant agent use in HCV-mixed cryoglobulinaemia
- Describe the use of steroids immunosuppressant agents and plasmapheresis

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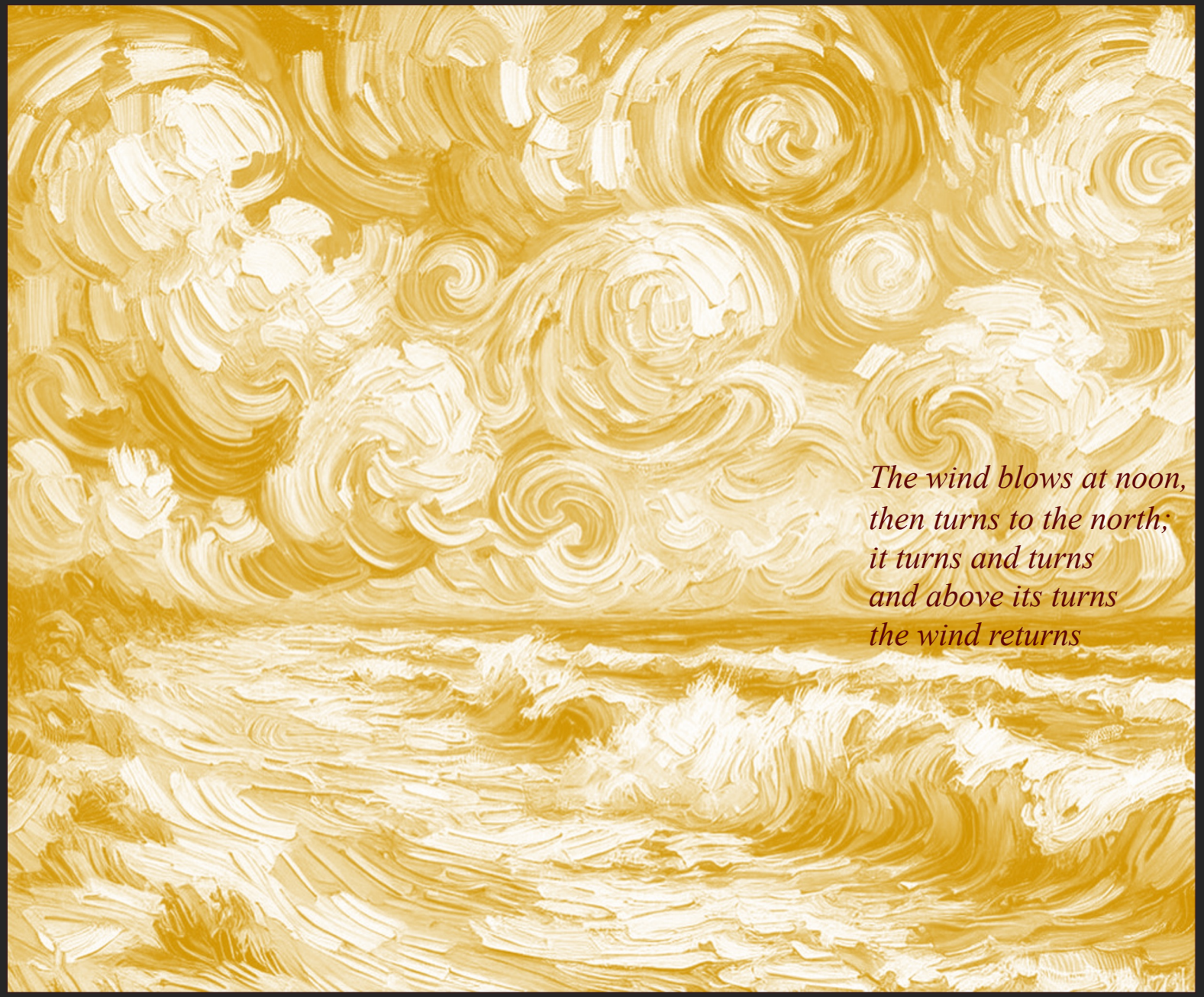

Vanity of vanities,
says Qohelet.
Vanity of vanities,
all is vanity!